Prehospital dyspnoea measurements

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LIST OF PAPERS

This thesis is a summary of the three following papers:

Paper I
Lindskou TA, Pilgaard L, Søvsø MB, Kløjgård TA, Larsen TM, Jensen FB, Weinreich UM, Christensen EF. Symptom, diagnosis and mortality among respiratory emergency medical service patients. PLoS One [Internet]. 2019;14(2):e0213145. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30817792

Paper II
Lindskou TA, Weinreich UM, Lübcke K, Kløjgaard TA, Laursen BS, Mikkelsen S, Christensen EF. Patient experience of severe acute dyspnoea and relief during treatment in ambulances: A prospective observational study. UNDER REVIEW, November 2019. Scand J Trauma Resusc Emerg Med.

Paper III
Lindskou TA, Lübcke K, Kløjgaard TA, Laursen BS, Mikkelsen S, Weinreich UM, Christensen EF. Predicting outcome for ambulance patients with dyspnoea – a prospective cohort study. SUBMITTED

ENGLISH SUMMARY

Acute dyspnoea is a severe and complex symptom, but knowledge of the patient's characteristics, perceived dyspnoea and if they experience a relief of symptom is limited. Studies assessing perceived dyspnoea in the prehospital setting are scarce, as are studies investigating the relation between acute dyspnoea, objective measurements, and patient outcome. Hence the objective of this thesis was to characterize ambulance patients with acute dyspnoea and investigate their initial perceived intensity of the symptom and whether they experience a relief hereof. Finally, to assess the clinical usefulness of a verbal numerical rating scale for assessing the patients' perceived acute dyspnoea (dyspnoea scale).

We carried out three studies, *study 1* investigated characteristics of ambulance patients with acute dyspnoea as assessed at the emergency call. *Study 2* investigated patients' perceived intensity of acute dyspnoea, relief hereof, and relation to objective measurements (vital signs). *Study 3* assessed the dyspnoea scale's ability to predict patient outcome.

We found the ambulance patients with acute dyspnoea covered all ages, with the largest peak among the elderly. Patients brought to a hospital were primarily diagnosed with respiratory diseases, circulatory diseases, and unspecific diagnoses. 30-day mortality rate was 13 % and increased with age. The majority of the patients were able to use the dyspnoea scale and reported an initial high dyspnoea scale score that decreased during prehospital treatment. The dyspnoea scale scores were related to objectively measured vital signs and the scale contributed to predicting hospitalisation and stay at intensive care unit. Patients unable to use the dyspnoea scale had an increased likelihood of stay at intensive care unit and 30-day mortality rate.

The distribution of diagnoses emphasises the complexity of the symptom. The patient's' mortality rate, initially high perceived acute dyspnoea, and vital signs suggest acute dyspnoea is a severe symptom among ambulance patients. Increased focus on acute treatment of the patient group might influence the current trend in prevalence of patients and their outcome. The dyspnoea scale appears usable in the ambulance, relate to patients' vital signs, and contribute to predicting patient outcome. The dyspnoea scale may be beneficial for assessing effect of treatment, and contribute to existing or novel triage scoring systems, thereby improving the patient care pathway.

DANSK RESUME

Akut dyspnø er et alvorligt og komplekst symptom, men der er begrænset viden om hvem patienterne er, hvor intenst de oplever akut dyspnø og om de oplever en lindring heraf. Der findes kun få præhospitale studier som vurderer patienternes oplevelse af akut dyspnø. Det samme gør sig gældende for studier om forholdet imellem akut dyspnø, objektive målinger af akut dyspnø og hvordan det videre går patienterne (outcome). Målet med denne afhandling var at karakterisere ambulance patienter med akut dyspnø, undersøge intensiteten af deres akutte dyspnø og om de oplever en lindring heraf. Derudover at vurdere den kliniske brugbarhed af en verbal numerisk rangeringsskala til at vurdere patienternes akutte dyspnø (dyspnø skala)

Vi udførte tre studier, *studie 1* undersøgte karakteristika blandt ambulance patienter vurderet til at have akut dyspnø ved 1-1-2 opkaldet. *Studie 2* undersøgte hvor intenst patienterne oplevede akut dyspnø og om de oplevede en lindring heraf. Derudover om der var en sammenhæng mellem deres oplevede akutte dyspnø og objektive målinger fra ambulancen (vitalparametre). *Studie 3* vurderede dyspnø skalaens evne til at forudsige patienternes outcome.

Vi fandt at ambulance patienterne med akut dyspnø dækkede alle aldre, med den største gruppe blandt de ældre. Patienter som blev bragt til et hospital, blev primært diagnosticeret med sygdomme i åndedrætsorganer, sygdomme i kredsløbsorganer, og uspecifikke diagnoser. Patienternes 30 dage mortalitetsrate var 13 % og steg med alderen. Størstedelen af patienterne var i stand til at bruge dyspnø skalaen og angav en indledende høj intensitet af akut dyspnø som dog faldt under den præhospitale behandling. Dyspnø skalaen var relateret til vitalparametre, og bidrog til at forudsige hospitalisering og ophold på intensivafdeling. Patienter som ikke var i stand til at bruge dyspnø skalaen havde en øget sandsynlighed for ophold på intensivafdeling og 30 dages mortalitet.

Fordelingen af diagnoser understreger symptomets kompleksitet. Patienternes mortalitetsrate og høje intensitet af akut dyspnø fremhæver alvorligheden af akut dyspnø blandt ambulancepatienter. Et øget fokus på akut behandling af patienterne kunne påvirke den nuværende tendens i andelen af patienter og deres outcome. Dyspnø skalaen fremstår brugbar i ambulancerne, og kunne bruges til at vurdere effekt af behandling eller bidrage til eksisterende eller fremtidige triage scores og dermed bidrage til at forbedre patientforløbet.

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So again, thank you all for your assistance.

Your moſt humble ſervant,
Tim Alex Lindskou

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CHAPTER 1. INTRODUCTION

In 2018, the Danish Council on Ethics published a report on prioritisation in the Danish health services. [1] The council emphasised a considerable unjust prioritisation of patients, as the quality of care appear to depend on their specific disease. As such cancer patients appear to receive considerably more resources than patients suffering from chronic obstructive lung disease. [1]
Several studies regarding inequality in the Danish health care system has been published, among others concerning chronic obstructive lung diseases [2,3] and cancer [4], and especially socioeconomic status and education level appear to be at play [5–7]
A questionnaire including 410 medical doctors from hospitals, general practises and private specialist practises in Denmark also expressed this inequality, as more than half answered that they experience prioritisation of patients as random and unsystematic. [8]

The focus of this thesis is a patient group including many of the low prioritised patients, namely those with acute dyspnoea in the prehospital setting. The thesis may contribute in bringing more attention to these overlooked patients.

1.1. LITTERATURE SEARCH

To investigate existing literature regarding dyspnoea in the prehospital setting, we conducted a systematic literature search. We initially identified aspects of the project and gathered search terms for each of the research subject with inspiration from the PICO approach as far as it was possible (e.g. **P**opulation: *prehospital dyspnoea patients*, **I**ntervention: *dyspnoea measurements, verbal numerical rating scale*, **C**omparison: none, **O**utcome: *mortality, symptoms, diagnosis*). The search terms within each aspect (including both single words, MESH-terms, phrases, and truncated terms) were combined with Boolean operator OR, and each aspect were combined with AND in PubMed.

Aspect dyspnoea	
Dyspnea	MESH term
dyspnoea	Text word
Dyspnea	Text word
shortness of breath	Text word
Breathlessness	Text word
difficult* AND breath*	Text word
breath shortness	Text word
Aspect prehospital	
Emergency Medical Services	MESH term
Emergency Medical Dispatch	MESH term
Emergency Medical Service Communication Systems	MESH term
Transportation of Patients	MESH term
Ambulance Diversion	MESH term
Ambulances	MESH term
Air Ambulances	MESH term
Stretchers	MESH term
Advanced Trauma Life Support Care	MESH term
pre-hospital	Text word
prehospital	Text word
ambulance*	Text word
emergency medical service*	Text word
out-of-hospital	Text word
HEMS	Text word
rapid response car	Text word

Example of identified aspects and search terms in the PubMed literature search for dyspnoea and the prehospital setting.

Our search strategy was revised to include broader terms as the initial search strings was too limiting for the specific research area.

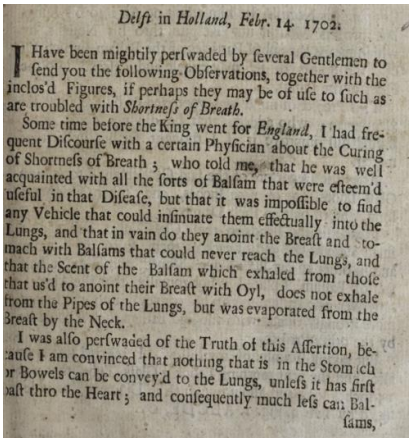
PubMed searches was supplemented by searches in Ovid Embase and Google Search. We also applied snowballing by following references in relevant articles.

CHAPTER 2. BACKGROUND

2.1. DYSPNOEA

The symptom dyspnoea is well known throughout time and it has had several definitions. [9–11] One of the earliest references in a scientific journal is Anthony van Lewuenhoeck's letters to the Philosophical Transactions of the Royal Society of London in 1703, describing a glass tube to infuse balsam into the lungs of patients troubled with shortness of breath. [9] In general dyspnoea is described as an unpleasant distressing experience of discomfort when breathing that can vary in intensity, and is can be differentiated into acute and chronic dyspnoea. [11] It is specifically the acute dyspnoea that is our focus in this thesis. Not only patients with respiratory diseases suffer from dyspnoea, it is a symptom present in many underlying diseases and as such also common in cardiovascular diseases [11–14] Is complex as it has a multidimensional nature where physical, psychological, social aspects, and others may both be affected by and affect dyspnoea. [12,15,16] Objective measurements such as respiratory rate, blood oxygen saturation or peak expiratory flow can be used to assess dyspnoea, but as a symptom only the patient can perceive it, and there appears to be a limited relation between objective measurements and perceived dyspnoea, as previous studies have found conflicting results. [12,17,18]

Likewise, it is difficult to assess the relation between objective measures of acute dyspnoea and patient outcome. Respiratory rate has previous been suggested to be related to acute dyspnoea relief and thereby reduced likelihood of hospitalisation and mortality. [19] Acute dyspnoea as a symptom by itself, has also been found to be related to an increased likelihood of hospitalisation and mortality within one year, among emergency department patients. [20]



Delft in *Holland*, *Febr.* 14. 1702.

I Have been mightily perſwaded by ſeveral Gentlemen to ſend you the following Obſervations, together with the inclos'd Figures, if perhaps they may be of uſe to ſuch as are troubled with *Shortneſs of Breath*.

Some time before the King went for *England*, I had frequent Diſcourſe with a certain Phyſician about the Curing of Shortneſs of Breath; who told me, that he was well acquainted with all the ſorts of Balſam that were eſteem'd uſeful in that Diſeaſe, but that it was impoſſible to find any Vehicle that could inſinuate them effectually into the Lungs, and that in vain do they anoint the Breaſt and Stomach with Balſams that could never reach the Lungs, and that the Scent of the Balſam which exhaled from thoſe that us'd to anoint their Breaſt with Oyl, does not exhale from the Pipes of the Lungs, but was evaporated from the Breaſt by the Neck.

I was alſo perſwaded of the Truth of this Aſſertion, becauſe I am convinced that nothing that is in the Stomach or Bowels can be convey'd to the Lungs, unleſs it has firſt paſt thro the Heart; and conſequently much leſs can Balſams,

Early publication in a scientific journal concerning shortness of breath, i.e. dyspnoea. From: II. Part of some letters from Mr Anthony van Lewuenhoeck, F. R. S. to the Royal Society, and the Right Honourable the Lord Somers their president, containing several microscopical observations and experiments concerning the animalcula in semine masculino . Philos Trans R Soc London. 1703;23(279):1137–51.

However, studies investigating the patient's own perception of dyspnoea and its relation to outcome, are scarce and have primarily investigated for chronic dyspnoea - even fewer have investigated acute dyspnoea, e.g. in the emergency department or intensive care unit. [21–23]

So, dyspnoea, much like pain, is highly subjective and can be difficult to assess. Previous studies have compared patients' own assessment of dyspnoea to assessments made by healthcare professionals and found poor agreement between the two, with the healthcare professionals underestimating the patients' dyspnoea further emphasising the importance of the patients' own experience of the symptom. [24,25] There are several tools that attempt to assess dyspnoea, including unidimensional tools that can be used to quantify and describe the quality of the symptom. Likewise, multidimensional tools may include more aspects such as quality of life and emotional state. [26] Notable examples include:

The visual analogue scale, first described in 1921 as a graphic rating method for evaluating workers and since then well known in pain assessment research. Often shown as a 100 mm line with one extreme described as no breathing difficulty at all, and the other being the worst imaginable breathing difficulty. The patent may then mark or indicate their perceived dyspnoea on the 100 mm line. [27–29]

The MRC dyspnoea scale, described in 1952 for assessing the severity of dyspnoea. Grades breathlessness from 1 to 5 at exertion and is used alongside a questionnaire on respiratory symptoms when performing epidemiological studies on larger groups. The questionnaire latest revision was in 1986 and include questions regarding phlegm, smoking, and coughing among others. [30–32] The Medical Research Council require credit when the MRC dyspnoea scale is used. Modified versions are commonly used.

The Borg scale of perceived exertion, developed in 1982 as a combination of verbal descriptions of breathing and a numerical 6 to 20 scale for rating breathlessness during activity. It is most commonly used in the modified version with a 0 to 10 scale and accompanying verbal descriptors.[17,33,34]

Yet many tools are intended for dyspnoea during activity or related to chronic diseases, and few are intended for acute dyspnoea in a clinical setting though more have emerged. Although some tools are commonly used for specific patient groups, previous reviews have not found which tool should be considered the golden standard, when assessing dyspnoea in different settings. [26,35–37] Unidimensional scales, e.g. verbal numerical rating scales that are fast to use and easy to understand, have in previous studies been suggested as a tool to assess the severity of acute dyspnoea in emergency departments, and some studies have already done so. [18,26,38,39]

Summary: *Acute dyspnoea is a severe and complex symptom present in many underlying diseases. There is limited relation between objective measurements and the acute dyspnoea perceived by the patient. Several tools are available for assessing dyspnoea, but few have been used in the prehospital setting. Relation between objective measurements of dyspnoea and patient outcome is suggested, but studies investigated whether there is a relation between the patients' perceived acute dyspnoea and patient outcome are limited.*

2.2. THE DANISH PREHOSPITAL SETTING

The following section is a short presentation of the Danish prehospital setting. We have described the setting in the publication *The Danish prehospital emergency healthcare system and research possibilities*, which can be read for further details. [40]

Danish legislation states the following regarding emergency medical services:

> "**The purpose of the prehospital effort is to save lives, improve health prospects, relieve pain and other symptoms, shorten the overall duration of illness, and provide care and safety"** [41]

When an emergency number, 1-1-2, call is made, it is answered by the police (and by the Copenhagen fire brigade for the Capitol Region of Denmark only). The call is forwarded to one of the five the regional Emergence Medical Coordination Centre if it is health related. [40] The call is here answered by healthcare professionals that assess the situation and adequate response with the aid of the criteria based dispatch tool Danish Index for Emergency Care (DI). [42] The DI is divided into 37 criteria, which amongst others include incidents (e.g. *traffic accident, and diving accident*) symptoms (e.g. *breathing difficulties,*

cramps, decreased consciousness – paralysis - dizziness), and others (e.g. *possible deceased*) [42] Each criteria is specified with suggested response urgency and type of vehicle/personnel.

Danish ambulance personnel do not only transport patients, but provide treatment and medication, e.g. oxygen, salbutamol for patients with chronic obstructive lung disease or asthma, and intubation by prehospital anaesthesiologists with mechanical ventilation started in the ambulance. [43–46] Among the available equipment in the ambulances is the electronic prehospital medical record in the form of a tablet computer, where treatments and measurements can be entered. [40] Vital signs, such as blood oxygen saturation, blood pressure and heart rate, can be measured automatically and send directly to the prehospital medical record, by a portable defibrillator/monitor present in the ambulance. [40,47]

The portable tablet computer with the electronic prehospital medical record

Summary: *The purpose of Danish emergency medical services is to save lives, improve health prospects, relieve pain and other symptoms, shorten the overall duration of illness, and provide safety and care. Patients are initially assessed over the phone by healthcare professionals who use the Danish Index for Emergency Care. Ambulance professionals provide treatment to patients and register data in the electronic prehospital medical record.*

2.3. ACUTE DYSPNOEA IN THE AMBULANCES AND PREHOSPITAL SETTING

We know that acute dyspnoea is not uncommon in the prehospital setting. [48–50] Previous studies have assessed the percentage of calls to emergency medical services requesting an ambulance due to acute dyspnoea and found 6 - 7 % of calls in Switzerland [51], 9 % in Sweden [52], 7 % in Denmark [53–55], and 12 % to 19 % in United States of America. [49,56]

A study from Denmark study found a one- and one through 30-day mortality

rate of 5 % and 12 % among ambulance patients with acute dyspnoea at the time of the emergency call – a mortality rate only surpassed by patients either unconscious or with cardiac arrest at the emergency call. [53]
However, studies investigating characteristics of acute dyspnoea patients in the ambulance is limited.
A study from the United States of America included patients assessed as having respiratory distress by emergency medical service personnel. The study reported, amongst other, respiratory rate, oxygen saturation systolic blood pressure, heart rate, Glascow Coma Scale scores, and prehospital interventions for the patients [49]

We have previously investigated patients with ambulance contact in the same North Denmark Region setting as this thesis. The study found that 6 – 8 % of all ambulance patients brought to a hospital in the period 2007 – 2014, was diagnosed with respiratory diseases, making it the fifth most frequent diagnosis given in hospital among ambulance patients. [57] They had a one- and 30-day mortality rate of 3 % and 12 % respectively, amassing the second highest number of cumulative deaths among ambulance patients brought to a hospital [58] Despite an overall decrease in mortality for the ambulance patients, even reduced by half among patients diagnosed with cardiovascular diseases, no change in mortality was found for the patients with respiratory diseases during the 8-year period. [57]

Aside from ambulance patients, dyspnoea is also common in the emergency departments. A previous study from Australia, New Zealand, Singapore, Hong Kong, and Malaysia found 5 % of the emergency department patients presented with dyspnoea. [59] In Norway, shortness of breath was the fourth most commonly used diagnosis code, constituting 9 % of contacts. [60] A Danish from the same setting as the thesis, study found patients diagnosed with respiratory diseases amounted to up 5 % of the emergency department contacts, being the fifth most frequent diagnostic chapter. [61]

Summary: *We know that patients with acute dyspnoea is common in the ambulances and the patients have a continuous high mortality, but we do not know much about the patient's characteristics, perceived dyspnoea and if they experience a relief of symptoms.*

2.4. OBJECTIVE

Acute dyspnoea is a severe symptom, common in the ambulances and related to a high mortality. Little is known about acute dyspnoea patients' characteristics and perceived symptom in the ambulances. A verbal numerical rating scale might be useful for assessing the patients' perceived acute dyspnoea.

Consequently, the objective of this thesis was threefold:

- **The acute dyspnoea ambulance patient**
  Characterize ambulance patients with acute dyspnoea, in regard to age, sex, symptom at the emergency call, diagnosis given in hospital, and mortality.

- **Perceived dyspnoea in the ambulance**
  Investigate acute dyspnoea patients' initial perceived intensity of symptom in the ambulance, and whether they experience a relief of symptom.

- **Clinical usefulness of the dyspnoea scale**
  Assess the clinical usefulness of a verbal numerical rating scale for assessing the patients' perceived acute dyspnoea in the ambulance, as well as the scores possible relation to the patients' vital signs and outcome.

CHAPTER 3. METHODS

3.1. OVERVIEW

To fulfil the objective of the thesis, we conducted three studies with a following paper for each. The methods are described in detail in the papers but will be briefly presented in the following sections.

Study 1 concerned the characteristics and mortality of ambulance patients assessed as having acute dyspnoea at the emergency call. Secondarily, the study investigated the characteristics of ambulance patients diagnosed with respiratory diseases in hospital.

Study 2 investigated patients with acute dyspnoea in the ambulance's perceived intensity of dyspnoea and relief hereof with the use of a verbal numerical rating scale. Furthermore, the study investigated the relation between the perceived intensity and objective measured vital signs and assessed the scales usability.

Study 3 assessed the verbal numerical rating scale scores' ability to predict outcomes, namely hospitalisation for two or more days, intensive care unit stay, and mortality following the ambulance run.

3.2. SETTING

All three studies were carried out in the North Denmark Region, home to approximately 590 000 citizens spanning over a 7 900 km² area covering both rural and urban areas. [62,63] Emergency Medical Services North Denmark Region is responsible for emergency medical services in the region, and provide rapid response vehicles manned by paramedics, and mobile emergency care units manned with a paramedic and a prehospital anaesthesiologist. Ambulance services are contracted by Falck Denmark A/S. [40]

3.3. SELECTION OF PARTICIPANTS

In *study 1* we included ambulance patients who were assessed as having *breathing difficulties* according to DI at the emergency call. Furthermore, patients who were diagnosed within International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) chapter X, Diseases of the respiratory system (*respiratory diseases*) in hospital, following an emergency call. [64] Patients were included in the period January 2012 to September 2015 (**45 months**) [65]

For *study 2* and *study 3* we prospectively included ambulance patients over the age of 18, who had *breathing difficulties* according to DI, or acute dyspnoea as assessed by ambulance professionals. [66] The patients were included in the study during the period 1. July 2017 to 30. March 2019 (**21 months**) for *study 2*, and *study* 3 extended the period to 14. September 2019 (**26 months**). [66,67]

3.4. STUDY DESIGNS AND DATA SOURCES

Study 1

To describe the prehospital dyspnoea patient group, we carried out a population-based historic cohort study in *study 1*.

We obtained the ambulance patients' DI criteria at the emergency call from the logistic ambulance dispatch system (*EVA 2000, Falck Danmark A/S, Copenhagen, Denmark*). [65] Diagnoses given at hospital according to ICD-10, was retrieved from the regional Patient Administrative System. [68] Finally, we obtained patients' age, sex and time of death from the Danish Civil Registration System. [65]

Study 2

In *study 2* we conducted a prospective observational cohort study, to investigate prehospital dyspnoea patients' experienced intensity of dyspnoea, and assess the feasibility and clinical usefulness of a prehospital dyspnoea scale.

We implemented a verbal numerical rating scale, from heron referred to as dyspnoea scale, in the North Denmark Region ambulance service and had ambulance professionals ask patients to assess their dyspnoea using the scale. The ambulance professionals used the phrasing:

> ***"On a scale from 0 to 10, where 0 is no difficulties breathing at all and 10 is the worst possible breathlessness imaginable, how are you experiencing your breathing now?"*** (66)

Ambulance professionals asked the patients this question at their first contact to the patient, and at their last contact, i.e. prior to patient released on scene or transferred to hospital. We implemented the dyspnoea scale in the prehospital medical record, where the ambulance professionals entered dyspnoea scale scores alongside any other measurements and treatment given. If a patient was unable to use the score, either due to an acute situation, or due to language barriers or other, this was also registered by the ambulance professionals. Patients otherwise received normal treatment in the ambulances. (66)

We obtained dyspnoea scale scores, and vital signs measured in the ambulance (respiratory rate, blood oxygen saturation, blood pressure, and heart rate) from the electronic prehospital medical record. We retrieved logistic ambulance data from the logistic ambulance dispatch system Logis CAD (*Logis Solutions A/S, Nærum, Denmark*). Diagnoses given in hospital according to ICD-10, was obtained from the regional Patient Administrative System. Finally, patients' age and sex was obtained from the Danish Civil Registration System (66)

Study 3

We conducted a prospective cohort study to assess the dyspnoea scales ability to predict and contribute to predicting hospitalisation for two or more days, stay at intensive care unit within 48 hours, and mortality within 30 days of the ambulance run.

We included the same patients and data from *study 2*. We had a longer inclusion period, gaining more patients, and supplemented data with, date of death from the Danish Civil Registration System, and data on hospitalisation and intensive care unit stay from the regional Patient Administrative System. (66,67)

3.5. ANALYSIS

We used Stata/MP 15.1 (*StataCorp LLC, College Station, Texas, United States of America*) for all analyses in *study 1* and *study 2*, and Stata/MP 16.0 for *study 3*.

Study 1

We described the characteristics of the ambulance patients with DI criteria *breathing difficulty* at the emergency call, and calculated crude 1- and 30-day mortality rates using the Kaplan-Meier estimator. If a patient had more than one ambulance run in the study period, we only included the patient's first contact in the mortality analysis. A secondary description and presentation of mortality rates were made for ambulance patients diagnosed with *respiratory diseases* in hospital.

Supplementary analysis

For this thesis, we performed an additional age adjusted mortality analyses for *study 1* by stratifying patients into age groups of 20 years intervals.

Study 2

We excluded patients unable to use the dyspnoea scale score from the analyses in *study 2*. Patients with more than one ambulance run in the study period were included in all analyses.

The distribution of the dyspnoea scale scores was assessed by investigating frequency, and we used Wilcoxon matched-pairs signed ranks tests to assess the change in score between the two measurements.

Furthermore, we assessed whether the first measured dyspnoea scale scores were related to vital signs measured in the ambulance, using linear regressions and inspecting scatterplots. The relation to vital signs were also assessed using delta measurements, i.e. the difference between the first and last measured dyspnoea scale scores and vital signs. [66]

Supplementary analysis

For this thesis, we furthermore investigated the difference in vital signs for patients able to use the dyspnoea scale and those unable, with the use of two-sample t-tests.

Study 3

We excluded patients with a dyspnoea scale score of 0, and if patients had more than one ambulance run in the period, we only used their first contact when assessing mortality. Patients assessed as unable to use the dyspnoea score was excluded from the prediction analyses.

We used machine learning through a five-fold cross-validation where data was randomised into five equal sized groups. A logistic regression was then carried out, with one group used as validation data set and the remaining four used as training data set, thereby providing 20 % of the validation results. [69] This was done five times, giving a combined 100 % validation results from the logistic models (Figure 1). [67]

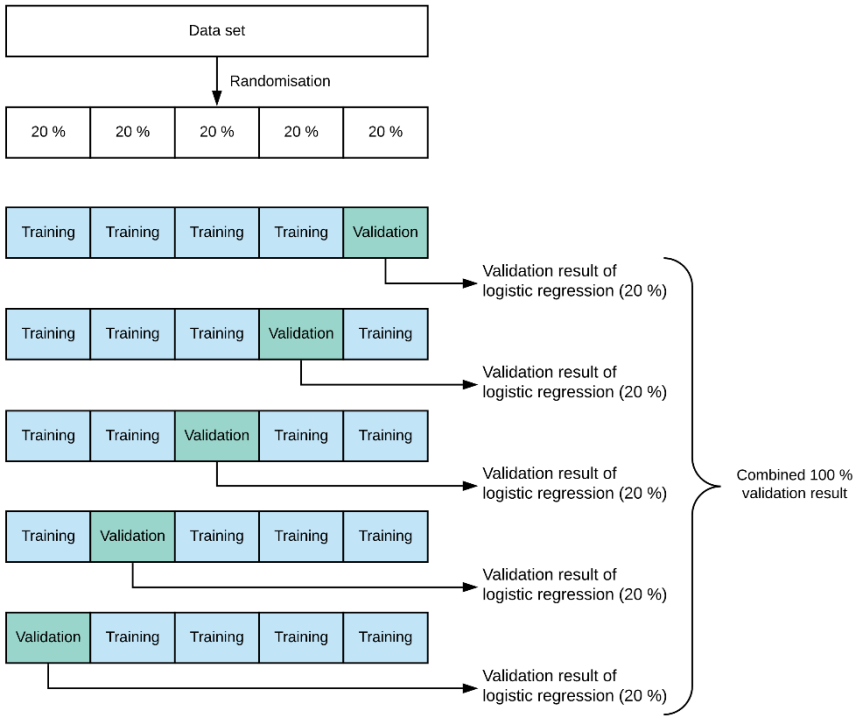


Figure 1: Example of the 5-fold cross-validation [67]

To predict outcome, we performed the five-fold cross-validation for each of the variables in Table 1. We also computed adjusted models using five-fold cross-validation for all variables combined, and all variables combined except for dyspnoea scale score.

Hospitalisation for more than two days	Intensive care unit stay within 48 hours	Mortality within 30 days
Age	Age	Age
Sex	Sex	Sex
First measured dyspnoea score	First measured dyspnoea score	First measured dyspnoea score
Delta dyspnoea score	Delta dyspnoea score	Delta dyspnoea score
First measured respiratory rate	First measured respiratory rate	First measured respiratory rate
Delta respiratory rate	Delta respiratory rate	Delta respiratory rate
First measured blood oxygen saturation	First measured blood oxygen saturation	First measured blood oxygen saturation
Delta blood oxygen saturation	Delta blood oxygen saturation	Delta blood oxygen saturation
First measured systolic blood pressure		
Delta systolic blood pressure		
First measured heart rate		
Delta heart rate		

Table 1: Variables included in the five-fold cross-validations. (67)

We drew receiver operating characteristic curves and calculated area under the curve (AUC) using the validation results from the five-fold cross-validations. (67,70)

We carried out a regression analysis for patients unable to use the dyspnoea scale to assess odds ratios for each outcome among these patients.

3.6. ETHICS

The studies were approved by the Danish Data Protection Agency (*study 1*: North Denmark Region record number 2008-58-0028 and project ID number 2016–80, *study 2* and *study 3*: North Denmark region record number 2008-58-0028 and project ID number 2017-128). Likewise, The Danish Patient Safety Authority approved access to prehospital patient medical records (*study 1*: 3-3013-1675/1, *study 2* and *study 3*: 1: 3-3013-2270/1).
Questionnaires, interviews and registry-based studies that does not involve biological material, do not require approval from the Committee on Health Research Ethics. (71) The project originally included interviews with patients who had used the dyspnoea scale, and the North Denmark Region Committee on Health Research Ethics was approached for approval to contact patients based on their diagnoses at the emergency department, i.e. related to breathing difficulty. The Committee on Health Research Ethics found the method to be exempt from requiring approval from the committee, but however reiterated the requirement of approval from the Danish Patient Safety Authority to access the patient medical records.

CHAPTER 4. RESULTS

I: THE ACUTE DYSPNOEA AMBULANCE PATIENT

We included 3 803 ambulance patients who had DI criteria *breathing difficulties* at the emergency call in the 45-month study period in *study 1*. In the secondary analyses of ambulance patients diagnosed with *respiratory diseases* in hospital, we included 4 014 patients (Figure 2). [65]

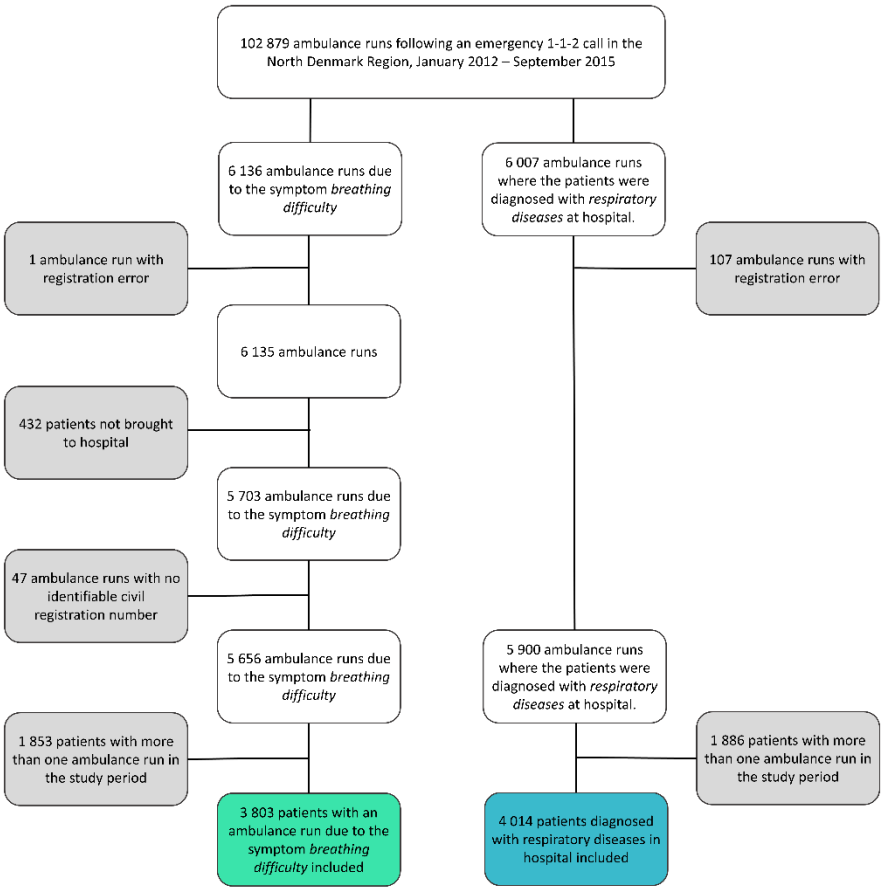
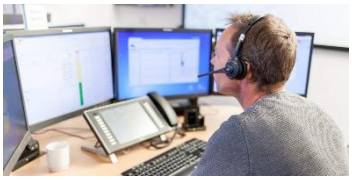


Figure 2: Flowchart of included patients in study 1. [65]

Patients with breathing difficulty at the emergency call



Healthcare professional at the North Denmark Region Emergency Medical Coordination Centre

We found the patients with DI criteria *breathing difficulties* at the emergency call had a median age of 69 years, 50 % were female, and they were primarily diagnosed with *respiratory diseases* in hospital (47 % of the patients). ICD-10 chapter IX, Diseases of the circulatory system (*circulatory diseases*) was the second most frequent symptom (13 %), followed by the two unspecific ICD-10 chapters XVIII, Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (*symptoms and signs*) and XXI, Factors influencing health status and contact with health services (*other factors*), with a combined 22 % (Figure 3). [65]

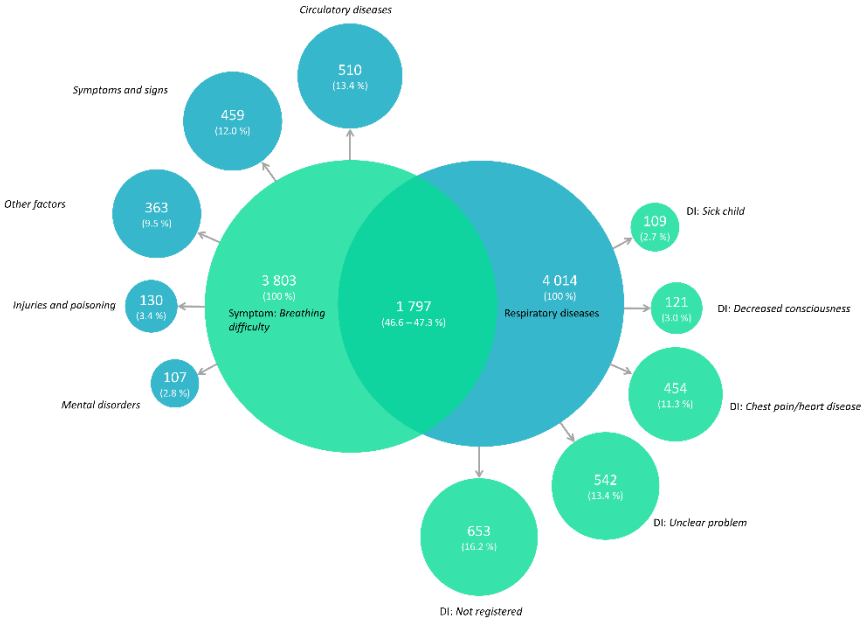


Figure 3: DI criteria and hospital diagnoses. The DI criteria given at the emergency call (green) and the diagnosis given to these patients in hospital (blue) and vice versa in study 1. [65]

The most frequent diagnostic code given under the *symptoms and signs* main chapter were specifically related to breathing difficulty, with 31 % receiving the code *R060 dyspnoea* (4 % of all patients) and 20 % *R064 hyperventilation* (2 % of all patients) (Table 2).

Diagnoses	N	Percent
Respiratory diseases	**1 797**	**47.25**
J441: Chronic obstructive pulmonary disease with acute exacerbation, unspecified	459	25.54
J189: Pneumonia, unspecified	363	20.20
J449: Chronic obstructive pulmonary disease, unspecified	185	10.29
J960: Acute respiratory failure	132	7.35
J459: Asthma, unspecified	110	6.12
Circulatory diseases	**510**	**13.41**
I509: Heart failure, unspecified	57	11.18
I489: Atrial fibrillation or atrial flutter, unspecified	53	10.39
I214: Non-STEMI	36	7.06
I219: Acute myocardial infarction, unspecified	31	6.08
I269A: Pulmonary embolism, unspecified	30	5.88
Symptoms and signs	**459**	**12.07**
R060: Dyspnoea	143	31.15
R064: Hyperventilation	91	19.83
R074: Chest pain, unspecified	33	7.19
R539F: Malaise	25	5.45
R559: Syncope or collapse	18	3.92
Other factors	**363**	**9.55**
Z039: Observation for suspected disease or condition, unspecified	229	63.09
Z038: Observation for other suspected diseases and conditions	36	9.92
Z768: Persons encountering health services in other specified circumstances	21	5.79
Z035: Observation for other suspected cardiovascular diseases	19	5.23
Z03: Medical observation and evaluation for suspected diseases and conditions	11	3.03
Injuries and poisoning	**130**	**3.42**
S202: Contusion of thorax	18	13.85
S223: Fracture of rib	11	8.46
T783: Angioneurotic oedema	5	3.85
S060: Concussion	4	3.08
T784: Allergy, unspecified	4	3.08
Mental disorders	**107**	**2.81**
F100: Mental and behavioural disorders due to use of alcohol : acute intoxication	23	21.50
F419: Anxiety disorder, unspecified	18	16.82
F410: Panic disorder [episodic paroxysmal anxiety]	10	9.35
F102: Mental and behavioural disorders due to use of alcohol : dependence syndrome	7	6.54
F101: Mental and behavioural disorders due to use of alcohol : harmful use	5	4.67
Remaining	**437**	**11.49**
Total	**3 803**	**100**

Table 2: Specific diagnoses for patients calling the emergency number with DI breathing difficulties. Includes the five most frequent ICD-10 main chapters and the five most frequent specific diagnostic codes for each chapter respectively. (65)

The prevalence of *respiratory diseases* and *circulatory diseases* increased with age, whereas patients diagnosed within ICD-10 chapter XIX, Injury, poisoning and certain other consequences of external causes (*injuries and poisoning*) and chapter V, Mental and behavioural disorders (*mental disorders*) were more prevalent in younger patients (Figure 4). (65)

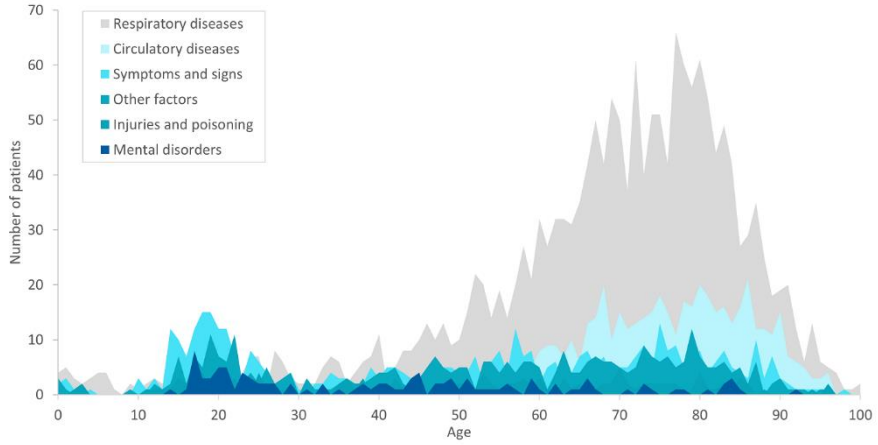


Figure 4: Hospital diagnoses and age. Age distribution of diagnoses given in hospital to patients assessed as having DI breathing difficulties at the emergency call in study 1. [65]

For patients with DI criteria *breathing difficulties* at the emergency call we found an overall 30-day mortality rate of 13 %, those diagnosed with *circulatory diseases* in hospital had the highest 30-day mortality rate with 18 %. Patients diagnosed with *respiratory diseases* had the second highest mortality rate with 13 %, followed by *other factors* and *symptoms and signs* with 9 % and 6 % respectively.
There were 1 853 patients with more than one ambulance run in the study period (33 %). [65]

We carried out a supplementary mortality analysis on the patient group with DI criteria *breathing difficulties*, stratified into age groups for this thesis. The supplementary analyses showed mortality increased with patient age (Table 3 and Figure 5).

Age	Patients	Deaths	Mortality rate (%, CI)
0 - 19	251	1	0.00 (0.00 to 0.03)
20 - 39	345	4	0.01 (0.00 to 0.03)
40 - 59	645	52	0.08 (0.06 to 0.10)
60 - 79	1 626	210	0.13 (0.11 to 0.15)
80 <	936	213	0.23 (0.20 to 0.26)

Table 3: Number of cumulative deaths within 30 days, and 30-day mortality rate for patients with DI criteria breathing difficulties stratified into age groups.
CI, 95 % confidence interval.

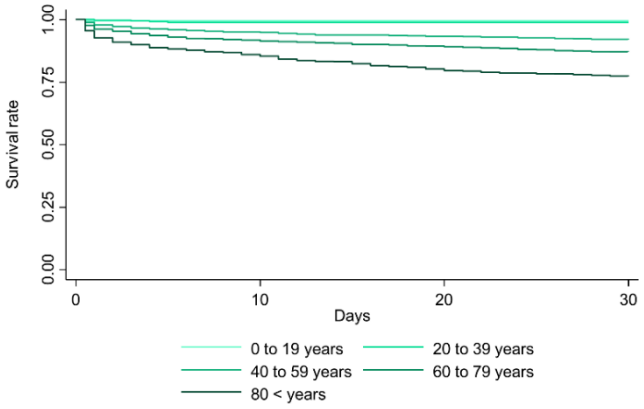


Figure 5: Kaplan-Meier survival curves for patients with DI criteria breathing difficulties stratified into age groups.

In *study 2,* we found similar results with a median age of 74 years, 51 % female patients, and 55 % diagnosed with *respiratory diseases*, 13 % with *circulatory diseases*, and 10 % with *symptoms and signs*. [66] *Study 2* included 3 199 patients assessed as having dyspnoea at the emergency call, or by the ambulance professionals upon seeing the patients, and 19 % had more than one ambulance run in the study period.

Study 3 also found results similar to *study 1* and *study 2*. The 2 461 included patients had a mean age of 70 years (range 18 to 104 years) and 50 % were female. Patients brought to a hospital was most frequently diagnosed with *respiratory diseases* (55 % of the patients), *circulatory diseases* (16 %), *symptoms and signs* (11 %) and *other factors* (6 %). [67]

Secondary: Patients diagnosed with respiratory diseases in hospital

Ambulances at the emergency department entrance at Aalborg University Hospital

We investigated patients diagnosed within ICD-10 chapter *respiratory diseases* in hospital, in *study 1*. The patients had a median age of 71 years and 46 % were female. They most frequently had DI criteria *breathing difficulties* (47 %) at the emergency call, followed by *unclear problem* (13 %) and *chest pain* (11 %). We found 16 % of the patients had no DI criteria registered (Figure 3). (65)

The number of patients with *breathing difficulties*, *unclear problem*, and *chest pain* increased with age, whereas *sick child* was the most frequent DI criteria among children (Figure 6). (65)

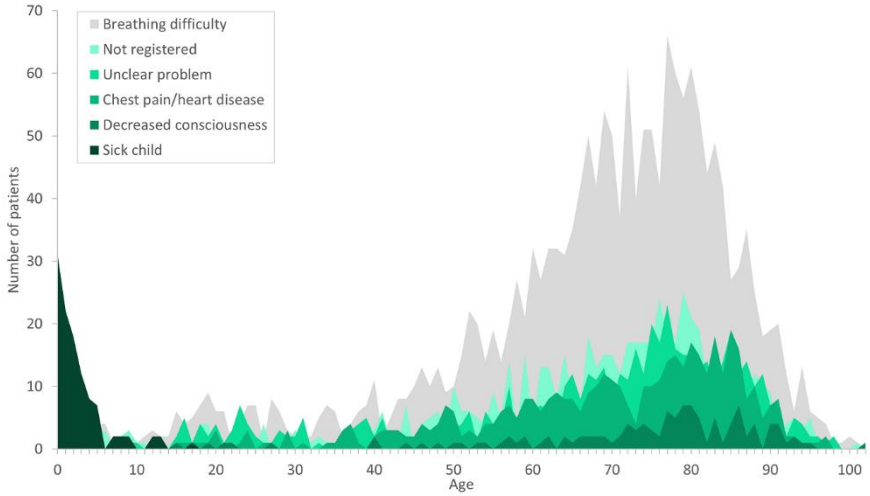


Figure 6: Hospital diagnoses and age. Age distribution of DI criteria given to patients diagnose with respiratory diseases in hospital, in study 1. (65)

Overall the patients diagnosed with *respiratory diseases* had a 30-day mortality rate of 13 %, those with DI criteria *decreased consciousness* at the emergency call had the highest 30-day mortality rate with 19 %, followed by *unclear problem* and *breathing difficulties* with 13 % each. (65)

As with patients with DI criteria *breathing difficulties*, we carried out a supplementary mortality analysis on the patient group diagnosed with *respiratory diseases*, stratified into age groups for this thesis. We found mortality increased with patient age (Table 4 and Figure 7)

Age	Patients	Deaths	Mortality rate (%, CI)
0 - 19	287	1	0.00 (0.00 to 0.02)
20 - 39	217	1	0.00 (0.00 to 0.03)
40 - 59	623	44	0.07 (0.05 to 0.09)
60 - 79	1 801	235	0.13 (0.12 to 0.15)
80 <	1 106	250	0.23 (0.20 to 0.25)

Table 4: Number of cumulative deaths within 30 days, and 30-day mortality rate for patients diagnosed with respiratory diseases stratified into age groups.
CI, 95 % confidence interval.

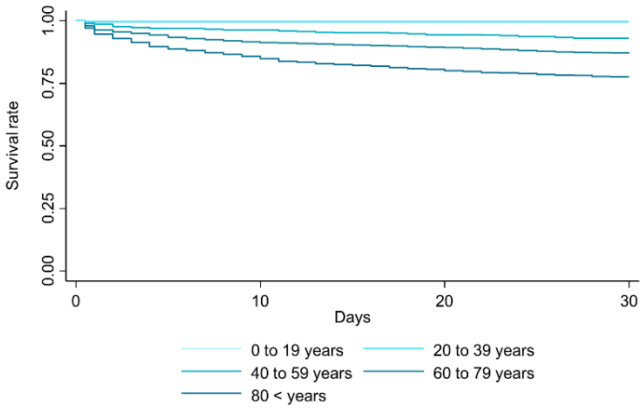


Figure 7: Kaplan-Meier survival curves for patients diagnosed with respiratory diseases stratified into age groups.

Summary: *Overall, we found the patients with DI criteria breathing difficulties at the emergency call, covered all age groups, with the biggest peak among the elderly. Half of the patients were female, and patients brought to a hospital were primarily diagnosed with respiratory diseases, circulatory diseases, and unspecific diagnoses in hospital. A 30-day mortality rate of 13 % were found for the patients diagnosed with respiratory diseases in hospital.* [65–67] *Mortality increased with age for the patients.*
Patients diagnosed with respiratory diseases in hospital, most frequently had DI criteria breathing difficulties, unclear problem, and chest pain at the emergency call. A peak in younger patients were observed for those with DI criteria sick child. Patients with breathing difficulties at the emergency call had an overall 30-day mortality rate of 13 % that increased with age. [65]

II: PERCEIVED DYSPNOEA IN THE AMBULANCES

In *study 2*, we included patients who were asked to assess their acute dyspnoea by ambulance professionals. There were 3 199 patients with at least one dyspnoea registration, 673 (21 %) of them were unable to use the dyspnoea scale and were excluded from the analysis. Of the 3 199 patients with at least one dyspnoea registration, 2 219 had two dyspnoea registrations and 122 (5 %) of them were registered as unable to use the dyspnoea score. These patients were excluded from the analysis. [66]

Patients had a median age of 74 years, 50 % were female, and 19 % had more than one ambulance run in the 21-month study period. [66]
The patients had an initial high degree of acute dyspnoea, with a median score of 8 (interquartile range 6 to 10) on the 0 to 10 dyspnoea scale. We found that among patients with two registered dyspnoea scale scores, 76 % had a significant decrease in score during prehospital treatment, from a median of 8 to a median of 4. Likewise, we found the score was unchanged for 17 % and increased for 2 % of the patients. (Figure 8). [66]

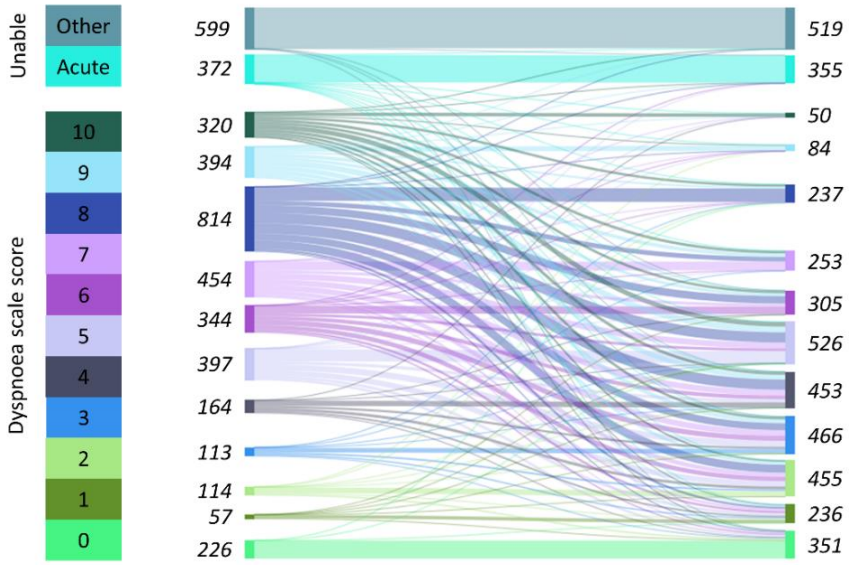


Figure 8: Dyspnoea scale scores. The distribution from the first to last measured dyspnoea scale scores in study 3. The figure includes patients unable to use the dyspnoea scale, who were excluded from the analysis.
Unable, patients unable to use the dyspnoea scale. Other, patients unable to use the score for all other reasons than severe medical situation. Acute, patients unable to use the dyspnoea scale due to acute medical situation.

The median change in dyspnoea scale scores for the individual patients were three points, and their change was most frequently two, three, and four points on the dyspnoea scale. (66)

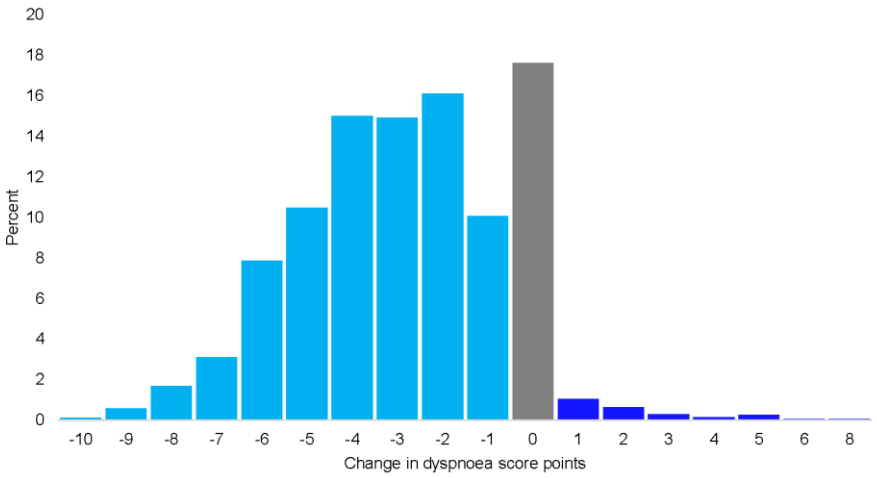


Figure 9: Change in score. The individual pointwise change in score for patients with two registered dyspnoea scale scores in study 2. (66)

Summary: *The ambulance patients with acute dyspnoea reported an initial high dyspnoea score that however decreased for the majority during prehospital treatment. The patients change in score was most prominently 2 to 4 points.* (66)

III: CLINICAL USEFULNESS OF THE DYSPNOEA SCALE

Usability by the patients

In *study 2*, we included 3 199 patients with at least one dyspnoea registration, 2 219 of which had two dyspnoea registrations.

We found 21 % of the patients with one dyspnoea registration were registered as unable to use the dyspnoea scale, 10 % due to acute situation and 11 % due to all other reasons. For patients with two dyspnoea registrations 5 % were unable, 3 % due to an acute situation and 2 % all other reasons. [66]

The patients used the full range of the dyspnoea scale from 0 to 10 and patients scoring 0 or 10, i.e. flooring- and ceiling, did not exceed 9 % at any measurement. [37,66,72] As mentioned above the patients individual change in score had a median of three (Figure 9). [66]

Relation to objective measured vital signs

We included 3 199 patients with at least one dyspnoea registration in *study 2*, of which 2 219 had two registrations. Patients registered as unable to use the dyspnoea scale was excluded (673 of patients with one dyspnoea registration and 122 of patients with two dyspnoea registrations). The percentage of patients with either missing respiratory rate, blood oxygen saturation, blood pressure or heart rate measurements did not exceed 4 %. Time between the dyspnoea scale score measurement and vital signs had a median of 2.5 minutes (interquartile range 0.9 to 6.5 minutes) [66]

In our supplementary analysis for *study 2* we found patients had a mean respiratory rate of 24 breaths per minute and blood oxygen saturation of 91 %. Patients unable to use the dyspnoea scale due to an acute medical situation had statistically significant higher respiratory rate and heart rate, as well as lower blood oxygen saturation and blood pressure compared to patients able to use the dyspnoea scale (Table 5).

	With score	Acute	Other
Respiratory rate	24 (6.8)	27 (9.4)*	23 (6.3) *
Blood oxygen saturation	91 (8.3)	90 (8.8)*	93 (7.7) *
Systolic blood pressure	149 (28.6)	143 (35.3)*	138 (27.2) *
Diastolic blood pressure	84 (19.2)	82 (26.0)	77 (17.4) *
Heart rate	97 (22.6)	102 (26.6)*	92 (21.4) *

Table 5: Supplementary analysis of patients unable to use the dyspnoea scale. Includes mean and standard deviation for each vital sign.
** statistically significantly different from the patients able to use the dyspnoea scale, two-sample t-tests.*
With score, patients able to use the dyspnoea scale. Acute, patients unable to use the dyspnoea scale due to an acute medical situation. Other, patients unable to use the dyspnoea scale due to all other reasons.

We found a significant relation between the first measured dyspnoea scale score and first measured vital signs, with the dyspnoea scale score rising with all vital signs except for blood oxygen saturation where it fell (Figure 10). [66]

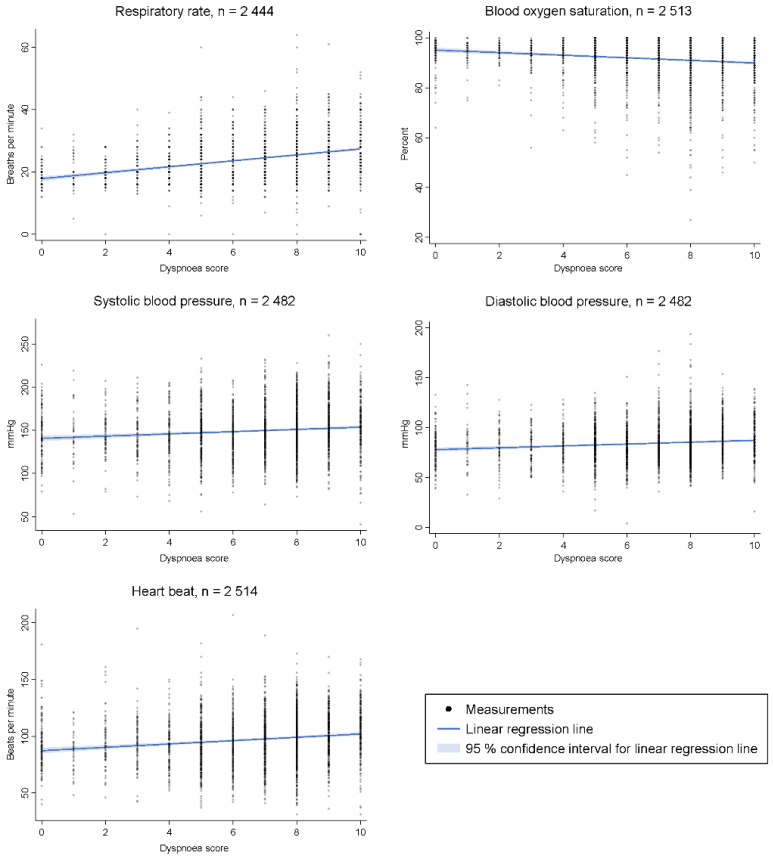


Figure 10: Dyspnoea scores and vital signs. Association between first measured dyspnoea scores and vital signs in study 2. [66]

Likewise, we also found a significant relation between the delta measurements (difference between the first and last measured dyspnoea scale scores and vital signs) with the delta dyspnoea scale score rising with delta vital signs, except delta blood oxygen saturation (Figure 11). [66]

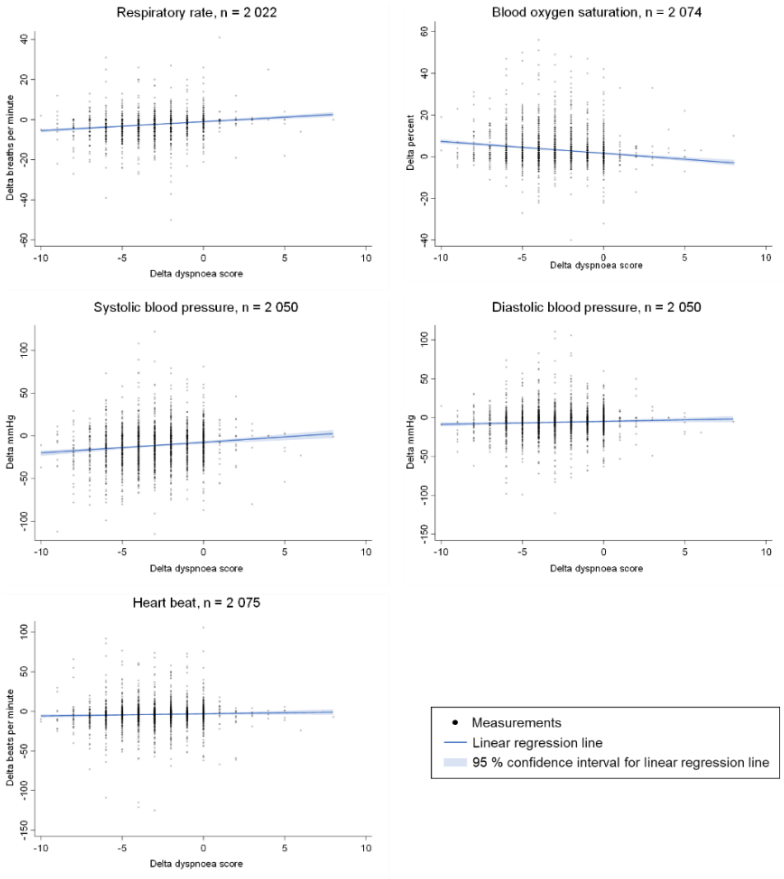


Figure 11: Delta dyspnoea scores and vital signs. Association between delta (the difference between first and last measured) dyspnoea scores and vital signs in study 2. [66]

Ability to predict patient outcome

In *study 3*, we included 3 144 patients who had a dyspnoea scale score above 0. The patients mean age was 70 years, 50 % were female, and 22 % had more than one ambulance contact in the 26-month study period. Less than 5 % of the vital signs were missing for any patient. [67]

Patients unable to use the dyspnoea scale

Patients unable to use the dyspnoea scale due to an acute medical situation had a significantly increased likelihood of stay at intensive care unit (odds ratio 3.25, 95 % confidence interval: 2.33 to 4.54) and 30-day mortality (odds ratio 2.89 (2.15 to 3.90)).

For patients unable to use the dyspnoea scale for other reasons, we found an increased likelihood of 30-day mortality (odds ratio 1.84 (1.40 to 2.43)).

Acute dyspnoea score and prediction of hospitalisation

The first measured dyspnoea scale scores were outperformed by the first measured blood oxygen saturation, first measured respiratory rate, age, and first measured heart rate when predicting hospitalisation (Table 6). [67]

Hospitalisation for more than two days	**Observations**	**AUC (95 % CI)**
All variables	**2 963**	**0.71 (0.69 to 0.73)**
All variables excluding dyspnoea scores	**2 963**	**0.71 (0.69 to 0.73)**
First measured blood oxygen saturation *(%)*	2 963	0.65 (0.63 to 0.67)
First measured respiratory rate *(breaths per minute)*	2 963	0.60 (0.58 to 0.62)
Age	2 963	0.60 (0.57 to 0.62)
First measured heart rate *(beats per minute)*	2 963	0.57 (0.55 to 0.59)
First measured dyspnoea score	2 963	0.56 (0.54 to 0.58)
Delta blood oxygen saturation *(%)*	2 963	0.56 (0.54 to 0.58)
First measured systolic blood pressure *(mmHg)*	2 963	0.53 (0.51 to 0.55)
Delta systolic blood pressure *(mmHg)*	2 963	0.52 (0.50 to 0.54)
Delta respiratory rate *(breaths per minute)*	2 963	0.51 (0.49 to 0.53)
Sex	2 963	0.51 (0.49 to 0.53)
Delta heart rate *(beats per minute)*	2 963	0.49 (0.47 to 0.52)
Delta dyspnoea score	2 963	0.49 (0.47 to 0.51)
Stay at intensive care unit within 48 hours of the ambulance run		
All variables	**2 998**	**0.73 (0.69 to 0.77)**
All variables excluding dyspnoea scores	**2 998**	**0.70 (0.66 to 0.75)**
First measured blood oxygen saturation *(%)*	2 998	0.65 (0.60 to 0.70)
First measured respiratory rate *(breaths per minute)*	2 998	0.61 (0.57 to 0.66)
First measured dyspnoea score	2 998	0.58 (0.53 to 0.62)
Delta dyspnoea score	2 998	0.57 (0.53 to 0.62)
Delta blood oxygen saturation *(%)*	2 998	0.53 (0.48 to 0.58)
Age	2 998	0.52 (0.47 to 0.56)
Sex	2 998	0.51 (0.46 to 0.56)
Delta respiratory rate *(breaths per minute)*	2 998	0.50 (0.45 to 0.55)
Mortality within 30 days		
All variables	**2 298**	**0.71 (0.67 to 0.75)**
All variables excluding dyspnoea scores	**2 298**	**0.71 (0.67 to 0.75)**
Age	2 298	0.66 (0.63 to 0.70)
First measured blood oxygen saturation *(%)*	2 298	0.64 (0.60 to 0.68)
Delta blood oxygen saturation *(%)*	2 298	0.56 (0.52 to 0.60)
First measured respiratory rate *(breaths per minute)*	2 298	0.53 (0.49 to 0.57)
Delta respiratory rate *(breaths per minute)*	2 298	0.52 (0.48 to 0.56)
Sex	2 298	0.51 (0.47 to 0.55)
Delta dyspnoea score	2 298	0.47 (0.43 to 0.51)
First measured dyspnoea score	2 298	0.46 (0.41 to 0.50)

Table 6: Result of the five-fold cross-validations for each individual and combined variables, for each of the three outcomes in study 3. [67]

The AUC did not change when adding dyspnoea scale scores to the combined model including all variables (Table 6 and Figure 12 A). [67]

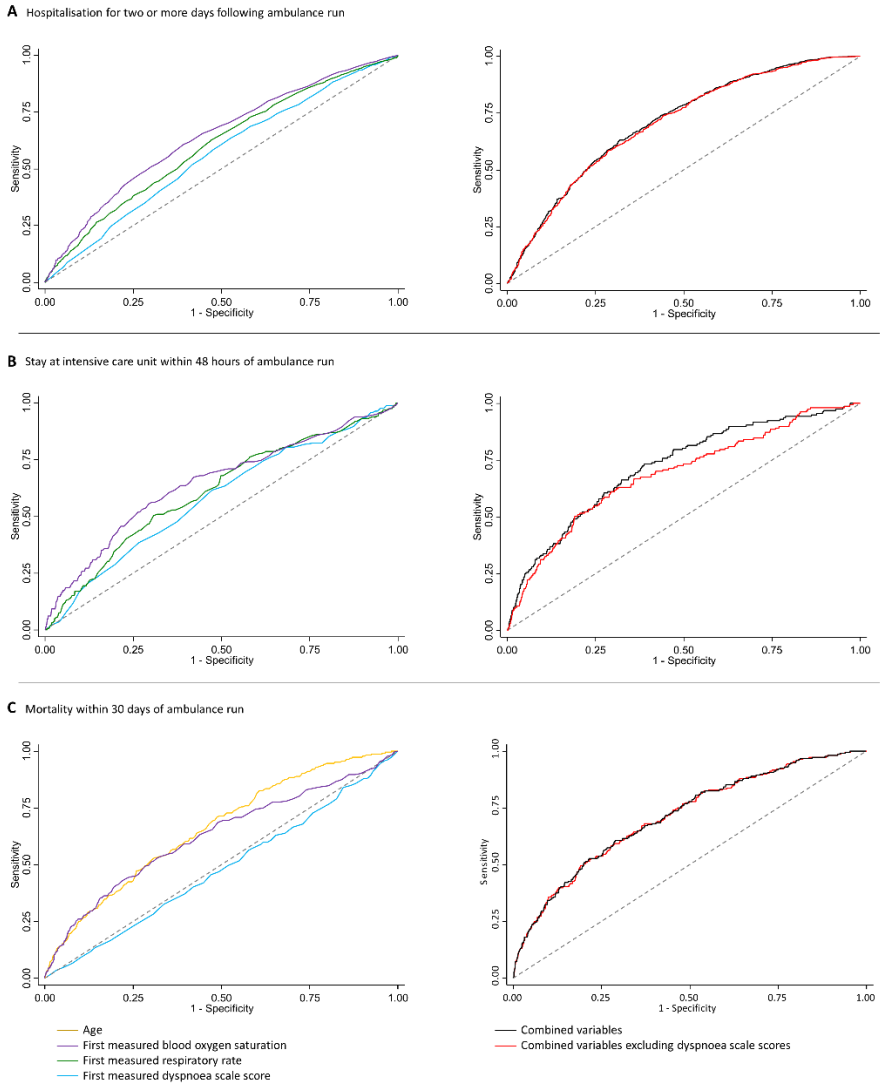


Figure 12: Receiver operating characteristic curves for each of the three outcomes in study 3. Includes the two independently best performing variables and the best performing dyspnoea scale score. Furthermore, the adjusted model with all variables combined, and all variables combined except for dyspnoea scale scores. (67)

Acute dyspnoea score and prediction of intensive care unit stay

For stay at intensive care unit, the first measured dyspnoea score had a lower AUC than the first measured blood oxygen saturation and first measured respiratory rate (Table 6). The AUC improved when adding the dyspnoea scale scores to the combined model containing all variables (Table 6 and Figure 12 B). [67]

Acute dyspnoea score and prediction of mortality

The dyspnoea scale performed close to an AUC of 0.5 when predicting mortality, and all other variables performed better (Table 6). Adding the dyspnoea scale measurements to the model including all variables did not change the AUC (Table 6 and Figure 12 C). [67]

***Summary*:** *The majority of the patients were able to use the acute dyspnoea scale, they used the full range of the scale with a median change of three points, and patients scoring 0 or 10 did not exceed 9 %.* [66]

Both the first measured and delta dyspnoea scale scores were related to the objectively measured vital signs. [66] *Patients unable to use the dyspnoea scale due to an acute medical situation had more severe means of vital signs compared to patients able to use the dyspnoea scale*

Patients unable to use the dyspnoea scale had a significant increased likelihood of stay at intensive care unit and 30-day mortality.
The dyspnoea scale had a low area under the curve when predicting hospitalisation but did however improve when predicting stay at intensive care unit. When added to adjusted models including all variables, the dyspnoea scale score contributed to predicting stay at intensive care unit. For predicting mortality, the dyspnoea scale had an area under the curve close to 0.5, and it had no impact when added to the adjusted model including all variables. [67]

CHAPTER 5. DISCUSSION

We found the follow results for each of the thesis' three objectives:

The acute dyspnoea ambulance patient

- Overall, we found the patients with DI criteria *breathing difficulties* at the emergency call, covered all age groups, with the biggest peak among the elderly. Half of the patients were female, and patients brought to a hospital were primarily diagnosed with *respiratory diseases*, *circulatory diseases*, and unspecific diagnoses in hospital. A 30-day mortality rate of 13 % were found for the patients diagnosed with respiratory diseases in hospital. Mortality increased with age for the patients.

- Patients diagnosed with respiratory diseases in hospital, most frequently had DI criteria breathing difficulties, unclear problem, and chest pain at the emergency call. A peak in younger patients were observed for those with DI criteria sick child. Patients with breathing difficulties at the emergency call had an overall 30-day mortality rate of 13 % that increased with age.

Perceived dyspnoea in the ambulances

- The ambulance patients with acute dyspnoea reported an initial high dyspnoea score that however decreased for the majority during prehospital treatment. The patients change in score was most prominently 2 to 4 points.

Clinical usefulness of the dyspnoea scale

- The majority of the patients were able to use the acute dyspnoea scale, they used the full range of the scale with a median change of three points, and patients scoring 0 or 10 did not exceed 9 %.

- Both the first measured and delta dyspnoea scale scores were related to the objectively measured vital signs. Patients unable to use the dyspnoea scale due to acute medical situations had more severe means of vital signs compared to patients able to use the dyspnoea scale.

- Patients unable to use the dyspnoea scale had a significant increased likelihood of stay at intensive care unit and 30-day mortality.
  The dyspnoea scale had a low area under the curve when predicting hospitalisation but did however improve when predicting stay at intensive care unit. When added to adjusted models including all variables, the dyspnoea scale score contributed to predicting stay at intensive care unit. For predicting mortality, the dyspnoea scale had an area under the curve close to 0.5, and it had no impact when added to the adjusted model including all variables.

5.1. STRENGTHS AND LIMITATIONS

Inclusion criteria

The large number of patients with complete follow-up included in all three studies were a major strength. However, we cannot be certain whether all acute dyspnoea patients were included, or if patients without acute dyspnoea were included, which introduces an inclusion bias. In s*tudy 1* we included both patients assessed at the emergency call and according to hospital diagnoses. [65] The assessment made over the phone may differ from the acutal condition of the patient met by the ambulance professionals, and thereby result in the inclusion of patients without dyspnoea. As *study 1* results suggest, patients with DI criteria other than *breathing difficulty*, may experience dyspnoea. [65] If patients with no acute dyspnoea were included, the mortality rates in *study 1* can be expected to be underestimated.

In *study 2* and *study 3* we included patients assessed both by healthcare professionals at the emergency call and by the ambulance professionals, in order to reduce the possible inclusion bias. [66,67] Furthermore, in *study 3* we excluded patients who had an initial dyspnoea scale score of 0, which may have further limited the inclusion bias. [67] We did not exclude patients with an initial dyspnoea scale score of 0 in *study 2*, as we investigated the relation between the full range of the dyspnoea scale scores and vital signs. [66]

Over the course of our three studies, we included patients in the period 2012 – 2019. Several changes in the prehospital setting has accoutred during this period of time; the DI have undergone several changes, as has the electronic prehospital medical record, and the population has aged. However, the age, percentage female patients, and distribution of diagnoses given in hospital, appear similar throughout our three studies. [65–67] This suggest the prehospital acute dyspnoea patients' characteristics have remined steady throughout the three study periods.

We included 3 199 patients with at least one dyspnoea registration in *study 2*, and 2 219 of them had two dyspnoea registrations. [66] We cannot say why a number of patients only had one dyspnea registration, and why more of them appeared unable to use the dyspnea scale (21 % in contrast to 5 % among patients with two registrations). [66] In *study 3* we found patients unable to use the dyspnoea scale had a significant increased likelihood of stay at intensive care unit and 30-day mortality. [67] The exclusion of patients unable to use the dyspnoea scale in *study 2*, therefore represent an inclusion bias as these patients must be expected to be in a most severe medical situation. [66]

Dyspnoea scale

The major strength in both *study 2* and *study 3* was the low number of missing vital signs and the presence of timestamps enabled us to obtain the vital signs measured closest to the registered dyspnoea score. [66,67]

However, the dyspnoea scale has the same limitation as many other dyspnoea assessment tools in regard to reliability (*i.e. are dyspnoea scale measurements consistent - similar measurement results under same conditions*) and validity (*do the dyspnoea scale measure dyspnoea as it is intended to do*). [37]

The ambulance patients with acute dyspnoea cannot be asked to assess their dyspnoea in two or more identical situation, which limits the options of testing the dyspnoea scales reliability.

Although a patients' perceived dyspnoea is not necessarily related to objective measurements due to other modalities affecting the perception of dyspnoea, we found a relation between the dyspnoea scale and vital signs in *study 2*. [66] This could indicate a certain construct validity to the dyspnoea scale.

In *study 3* we investigated the predictive validity of the dyspnoea scale, which was strengthen by the use of a five-fold cross-validation, maximizing the use of data for both training and validation. [67] Finally, the content validity of the dyspnoea score, i.e. does the dyspnoea scale incorporate all factors associated

with dyspnoea, might be limited. Other tools such as the Borg scale combines a 0-10 scale and verbal descriptors, possibly incorporating more dyspnoea related aspects. However, due to the acute ambulance setting it was not possible to incorporate several elements when assessing dyspnoea and the simple verbal numerical rating scale was therefore chosen. Yet, as the dyspnoea scale assess the patients' perceived dyspnoea, it can be considered whether this assessment implicitly incorporate all dyspnoea related factors into the perceived intensity. In general, several reliability and validity aspects were simply not possible in the acute prehospital setting, and clinical usefulness was therefore in focus for this project.

Including the patients themselves would be beneficial for assessing the dyspnoea scale's validity. Individual and focus group interviews could provide information of the patients experience of the scale and their intensity of acute dyspnoea. Likewise, focus group interviews with ambulance professionals could explore their experience with the use of the dyspnoea scale in the ambulance, through thematic coding.
We initially included patient interviews and informal interviews with ambulance professionals in the project. Patients brought to either the emergency department in the North Denmark Regional Hospital or the short-term stay unit at Aalborg University Hospital were interviewed as soon as they were stabilised following the ambulance run. However, several patients still had so laboured breathing that speaking came difficult. Interviewing patients at a later point in time would be beneficial, albeit risking recall bias.

Outcomes
For patients with more than one ambulance run in the study period, we only included the patients' first ambulance run for the mortality analyses in *study 1* and *study 3*. [61,67] This choice provided conservative estimates in contrast to if we had used the patients last contact - the mortality rates can therefore be considered as a minimum estimate. In *study 1* mortality was analysed using the Kaplan-Meier estimator and as such presented as crude estimates. However, our supplementary analysis showed mortality increased with age. [65] It is possible the mortality rates could shift further if adjusting for other variables such as comorbidity and history of smoking. Likewise, we did not adjust for these variables in *study 3*, as they are not normally available in the ambulance, and we aimed to assess the dyspnoea scales ability to predict outcome, thereby providing early identification of high-risk patients. [67]

Similarly, we did not stratify patients into more specific diagnosis groups in the mortality analysis in *study 1*. It is possible that the 30-day mortality rate would differ between these specific groups. As such it would be interesting to investigate the mortality rate e.g. for patients diagnosed with *J189 pneumonia*, the second most frequent specific diagnosis. [65] Likewise, we did also not stratify patients into diagnosis groups, or according to age when assessing the relation between the dyspnoea scale scores and vital signs in *study 2*. [66] We made this choice as *study 2* was an initial assessment of the dyspnoea scales abilities in a broad prehospital patient group with acute dyspnoea. Future studies further assessing the dyspnoea scale should investigate the effect of such variables as far as it is possible.

I: THE ACUTE DYSPNOEA AMBULANCE PATIENT

Regarding age and sex, we found that the acute dyspnoea ambulance patients appear to be among the elderly, with a median age of 69 and 74 years in *study 1,* 74 in *study 2*, and mean age of 72 years in *study 3*. [65–67] However, the patients covered all ages and the age distribution differed at ICD-10 chapter level and DI criteria level. [65] The age peaks we observed in *study* 1 appears similar to the peaks for all patients transported by an ambulance in the same setting in 2014, and to some degree patients with emergency department contact in the same region. [57,61] The percentage of female patients ranged from 46 % to 51 % in the three studies. [65–67]

A study from the United States of America included emergency medical service patients categorised as having respiratory distress by emergency medical service personnel in the period 2002 – 2006. Prekker et al. found, when excluding patients with traumatic injury or cardiac arrest, that patients had a mean age of 66 years, covered all ages from 18 to 100 years, and 59 % were female. [49] Likewise, an Australian and New Zealand study included ambulance patients who had dyspnoea as the main symptom when presenting to an emergency department in 2014. Kelly et al. found a median age of 74 years for the included patients, and 54 % were female. [48] These studies correspond to our findings in the three studies included in this thesis, emphasising the distribution of acute dyspnoea across all ages, but with a peak among the elderly, as well as the percentage of female patients.

When investigation the acute dyspnoea patients' diagnoses, approximately half of the patients received a diagnosis within ICD-10 chapter *respiratory diseases* (47 %) in hospital. The remaining patients received diagnoses within several different diagnostic chapters, with *circulatory diseases* (13 %), and the combined unspecific chapters *symptoms and signs* and *other factors* (22 %), being the most prominent. [65–67] *J441 chronic obstructive pulmonary disease with acute exacerbation* (12 % of the patients with DI criteria *breathing difficulties* at the emergency call) and *J189 pneumonia* (10 %) were the two most frequent specific diagnoses. [65] A previous study of patients admitted to a German emergency department found 5 % (third most frequent) of the patients were diagnosed with pneumonia. [73] Likewise a study investigation ambulance patients with dyspnoea admitted to an emergency department in Australia, New Zealand, Singapore, Hong Kong and Malaysia, found 23 % (the most frequent) were diagnosed with lower respiratory tract infection including pneumonia. [48]
The distribution of diagnoses among the prehospital dyspnoea patients emphasises the complexity of the symptom, as it is present in many underlying conditions. [14] These underlying conditions may present different experiences of dyspnoea and its effects. [15,16] Patients with lung cancer may therefore perceive dyspnoea differently than patients with chronic obstructive lung disease. [74,75]
Among the patients who received a diagnosis within the *symptoms and signs* chapter in *study 1*, we found the two most specific diagnoses given were *R060 dyspnoea* (4 % of all patients), and *R064 hyperventilation* (2 %). [76] Despite these two specific breathing related diagnoses, the patient group still cover several different specific diagnoses. Investigating the patient population from an even more detailed or grouped diagnostic level may therefore be beneficial for uncovering common patient characteristics and identify high-risk patients.

Regarding mortality, we found a 30-day mortality rate of 13 % in *study 1*. [65] A previous Danish study investigating mortality among emergency medical service patients. [53] Bøtker et al. found a 30-day mortality rate of 12 % for patients with acute dyspnoea at the emergency call, higher that patients with chest pain and trauma/accidents. [53] A Canadian study assessed the benefit of advanced life support in regard to mortality, among ambulance patients with shortness of breath. [77] Stiell et al. defined as the rate of death prior to a hospital discharge regardless of the duration of the admission. [77] Among patients receiving basic life support, Stiell et al. reported a mortality rate of 14 %, and 12 % for patients receiving advanced life support. [77]

These findings support the mortality rate we found in *study 1* and combined with the initial high dyspnoea score observed in *study 2*, this emphasises the severity of ambulance patients with acute dyspnoea. [65,66]

We found patients had a mean respiratory rate of 24 breaths per minute, that increased with the dyspnoea scale scores and blood oxygen saturation of 91 % that decreased with the dyspnoea scale scores. The patients included by Prekker et al., mentioned in the beginning of this section. had a mean respiratory rate 26 breaths and a mean oxygen saturation of 91 %. [49] Likewise, Kelly et al, also mentioned earlier, found a mean respiratory rate of 25 breaths, and a mean O2 saturation of 92.5. [48] Although these numbers may not appear severe, it is important to note it is means for broad patient groups with acute dyspnoea. It could be speculated that the prehospital dyspnoea patients contact EMS at a fairly late point in their medical situation, rather than prior to reaching the severe level indicated in our findings.

Finally we found the number of patients with more than one ambulance run ranged from 19 to 33 %. [65–67] A study from the United States of America investigated repeated ambulance users (six or more runs) and found the incidence of patients assessed as having respiratory problems at the emergency medical service incidence, was higher for repeated users, compared to non-frequent users. [78] A Danish study from the same region as the tree studies in this thesis, compared DI criteria and hospital discharge diagnoses for one-time- and repeated ambulance users (more than two ambulance runs) within 12-month periods. [79] Søvsø et al. found both patients with DI criteria *breathing difficulty*, and patients diagnosed with *respiratory diseases* were more frequent among repeated ambulance users than one-time ambulance users. [79] Furthermore, they found the diagnosis "other chronic obstructive pulmonary disease" occurred more frequent among repeated ambulance users (57 % in contrast to 23 % for one-time users). [79] Of all patients with DI criteria *breathing difficulty*, 12 % were diagnosed with *J441chronic obstructive pulmonary disease with acute exacerbation* and 5 % with *J449 chronic obstructive pulmonary disease* observed in *study 1,* might have contributed to the number of patients with more than one ambulance run. [65]

II: PERCIEVED DYSPNOEA IN THE AMBULANCE

In *study 2* we found ambulance patients with acute dyspnoea reported an initial high dyspnoea score with a median of 8. The score however decreased for the majority of the patients during prehospital treatment. Including emergency department patients with shortness of breath at admittance, a French study used both a verbal numerical- and visual scale to assess dyspnoea. [80] Placido et al. found the included patients had a median verbal numerical score of 7. [80] A study from Australia included emergency department patients with acute shortness of breath. Saracino et al. used a verbal numerical rating scale like the one used in *study 2* and *study 3* and found a median dyspnoea score of 6 when measuring dyspnoea scores of patients in the emergency department. [18] Furthermore, they observed a decrease in score from the initial measurement to 30 minutes later, from a median of 6 to 4. [18] The differences in scores compared to *study 2* could be due to the time of measurement. We included a broad prehospital acute dyspnoea patient group and obtained an initial dyspnoea score which in some case could be measured prior to any treatment, in contrast to patients' dyspnoea measurements in the emergency department by Placido et al. and Saracino et al. [18,66,80] This emphasises the severe intensity of acute dyspnoea initially experienced by the ambulance patients.

III: CLINICAL USEFULLNESS OF THE DYSPNOEA SCALE

Usability by the patients

When assessing the feasibility of using the dyspnoea scale in the ambulance and its clinical usefulness, we found 21 % of the patients with one dyspnoea registration were unable to use the dyspnoea scale, 10 % due to acute situation and 11 % due to all other reasons. For patients with two dyspnoea registrations 5 % were unable, 3 % due to the acute situation and 2 % all other reasons. [66] Our included patients in *study 2* and *study 3* were patients that had acute dyspnoea in connection to an ambulance contact, which can explain the number of patients unable to use the dyspnoea scale due to acute medical situations. [66,67]

All values on the scale were used with flooring- and ceiling not exceeding 9 %. A review investigated dyspnoea scores designed to assess acute respiratory distress severity and set a validation criterion as flooring and ceiling effects below 15 %, supporting the lack of these effects on the prehospital dyspnoea scale. [37,66,72]

The individual patient most frequently had a change of two to four points on the dyspnoea scale, suggesting a nuanced use by the patients.

Relation to objective measured vital signs

We found a statistically significant linear relation between the dyspnoea scale scores and vital signs measured in the ambulance in *study 2*. [66] Previous studies have found conflicting results regarding dyspnoea and objective measurements. The verbal dyspnoea score used by Saracino et al. was significantly related to respiratory rate, heart rate, and oxygen saturation. [18] Using a modified Borg scale in an emergency department, a study from the United States of America found the scale was related to oxygen saturation for patients suffering from asthma, but no correlation was found for patients with chronic obstructive lung diseases. [17] As such, the dyspnoea scale appears to have a relation to vital signs, but the conflicting results in previous studies suggest the dyspnoea scale score provides important information of the patients' subjective perceived dyspnoea that otherwise is unavailable.

Ability to predict patient outcome

In *study 3* we found the first measured dyspnoea scale score had an AUC of 0.56 when predicting hospitalisation, although it did not contribute when added to the adjusted model including all variables. [67] When predicting stay at intensive care unit, the first measured dyspnoea scale score had an ACU of 0.58, and contributed positively to the model, when added to the adjusted model including all variables. [67] An Australian study used a verbal numerical rating scale identical to the one in *study 2* and *study 3* and investigated its ability to predict dyspnoea patients departure from an emergency department. [22] Saracino et al. found the verbal dyspnoea score in combination with heart rate and mode of arrival (ambulance) could predict hospital admittance among the included patients. [22] The AUC reported by Saracino et al., exceeded those found in *study 3*, and the receiver operating characteristics curve crowded more towards the upper left corner. Saracino et al. identified optimal cut off points using 95 % confidence intervals of the means and forward stepwise regression to determine the best combination of variables to predict outcome, as well as inspected receiver operating characteristic curves to assess the dyspnoea scores ability to predict outcome on its own. [22] The different outcome measures, use of cut off points, and statistical method used by Saracino et al. account for the different results in our study.

The scope of *study 3* was to assess the dyspnoea scales possible effect in predicting outcome – as we found the dyspnoea scale had predictive abilities, the next step would be to follow Saracino et al.'s approach to identify cut off points and combination with other variables.
A Swiss study investigated the combination of common symptoms in an emergency department, e.g. dyspnoea and chest pain. [81] Kuster et al. found certain combinations of symptoms, amongst others dyspnoea and cough, were related to adverse outcomes. [81] The dyspnoea scale might in a similar manner be used in combination with other variables to contribute to existing prehospital triage tools used in the ambulance services, and other triage tools such as the National Early Warning Score and the Manchester Triage System. [82,83]

We found the dyspnoea scale scores ability to independently predict mortality was poor and did not contribute to the models including all variables in *study 3*. [67] A recent review investigated whether persistent dyspnoea was an independent predictor of mortality. [21] When controlling for age, smoking, and lung function, Pesola et al. found chronic dyspnoea to be an independent predictor of mortality in longitudinal studies. [21] The discrepancies between these studies and *study 3* can be explained by the inclusion of chronic dyspnoea in contrast to the patients with acute dyspnoea in our study, as well as the different measurement of dyspnoea.

CHAPTER 6. CONCLUSIONS AND PERSPECTIVES

6.1. CONCLUSIONS

We aimed to characterize the ambulance patients with acute dyspnoea and investigate their perceived dyspnoea. We found the patients spanned across all age groups, with the largest peak among the elderly, and approximately half of the patients were female. The patients were primarily diagnosed within ICD-10 main chapter *respiratory diseases*, but *circulatory diseases* and non-specific diagnoses were also prevalent, emphasising the complexity of the patient group. The patients' mortality rates, initially high perceived dyspnoea, and vital signs suggest that acute dyspnoea is a severe symptom among ambulance patients.

Furthermore, we aimed to assess the clinical usefulness of the dyspnoea scale. The patients' use of the dyspnoea scale suggest it is feasible to use in the ambulance, and it appears to be related to the patients' vital signs. The dyspnoea scale appears able to contribute to predicting the outcomes hospitalisation and stay at intensive care unit. Our findings suggest the dyspnoea scale provide patient information otherwise unavailable, i.e. the patients' perceived dyspnoea.

6.2. PERSPECTIVES

The prehospital patients with acute dyspnoea are a cause for concern. The greatly improved outcome for patients with cardiovascular diseases mentioned in the introduction, must be attributed to an increased effort and focus. Acute dyspnoea has a continued high mortality, it is extremely unpleasant for the patients who report an initial high degree of dyspnoea that however improve during prehospital treatment. A similar effort as with cardiovascular disease would most certainly aid the prehospital dyspnoea patients with acute dyspnoea. An increased focus on acute treatment of this patient group might be one approach that could influence the trend.
Regarding the dyspnoea scale the information provided could be beneficial in future clinical practice and research, e.g. for assessing effect of treatment as is currently done with pain scores.

It does also appear to contribute to prediction of the outcome stay at intensive care unit and to a lesser degree hospitalisation, which might be used to improve the patient care pathway. Further validation of the dyspnoea scale and possible interventional studies using the dyspnoea scale should be considered in the future.

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CHAPTER 8. APPENDICES

Appendix A. Paper I

Lindskou TA, Pilgaard L, Søvsø MB, Kløjgård TA, Larsen TM, Jensen FB, Weinreich UM, Christensen EF. Symptom, diagnosis and mortality among respiratory emergency medical service patients. PLoS One [Internet]. 2019;14(2):e0213145.

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PLOS ONE

RESEARCH ARTICLE

Symptom, diagnosis and mortality among respiratory emergency medical service patients

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Data Availability Statement: The data used in this study cannot be made publicly available as they contain sensitive patient identifying information. Data is available from the Danish Civil Registration System, the regional Patient Administrative System, and the Emergency Medical Services North Denmark Region, for researchers who are approved by the Danish Patient Safety Authority. Researchers interested in using data to replicate/verify the conclusions of the study, can therefore seek approval from the Danish Patient Safety Authority at https://stps.dk/da/

Abstract

Objective

Breathing difficulties and respiratory diseases have been under-reported in Emergency Medical Services research, despite these conditions being prevalent with substantial mortality. Our aim was two-fold; 1) to investigate the diagnostic pattern and mortality among EMS patients to whom an ambulance was dispatched due to difficulty breathing, and 2) to investigate the initial symptoms and mortality for EMS patients diagnosed with respiratory diseases in hospital.

Methods

Population-based historic cohort study in the North Denmark Region 2012–2015. We included two patient groups; 1) patients calling the emergency number with *breathing difficulty* as main symptom, and 2) patients diagnosed with *respiratory diseases* in hospital following an emergency call. Main outcome was estimated 1- and 30-day mortality rates.

Results

There were 3803 patients with the symptom *breathing difficulty*, nearly half were diagnosed with *respiratory diseases* 47.3%, followed by *circulatory diseases* 13.4%, *and symptoms and signs* 12.0%. The 1-day mortality rate was highest for *circulatory diseases*, then *respiratory diseases* and o*ther factors*. Over-all 30-day mortality was 13.2%, and the highest rate was for *circulatory diseases* (17.7%) then *respiratory diseases* and *other factors*. A total of 4014 patients were diagnosed with *respiratory diseases*, 44.8% had the symptom *breathing difficulty*, 13.4% *unclear problems* and 11.3%. *chest pain/heart disease*. 1-day mortality rates were highest for *decreased consciousness*, then *breathing difficulties* and *unclear*

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problem. Over-all 30-day mortality rates were 12.5%, the highest with symptoms of *decreased consciousness* (19.1%), then *unclear problem* and *breathing difficulty*. There was an overlap of 1797 patients between the two groups.

Conclusions

The over-all mortality rates alongside the distribution of symptoms and diagnoses, suggest the breathing difficulty patient group is complex and has severe health problems. These findings may be able to raise awareness towards the patient group, and thereby increase focus on diagnostics and treatment to improve the patient outcome.

Introduction

Background

Respiratory failure is one of the "First Hour Quintet" (alongside cardiac arrest, myocardial infarction, trauma, and stroke) which have been defined as the five time-critical conditions where immediate prehospital care by the Emergency Medical Services (EMS) yield the greatest effect, albeit rarely studied [1,2]. Dyspnoea, or breathing difficulty, can be the initial potential life-threatening symptom of respiratory failure, also emphasised by the Airway, Breathing, Circulation (ABC)–principle in emergency care [3,4]. However, breathing difficulty encompasses a variety of clinical conditions, often, but not always due to respiratory diseases. Previous studies have estimated that dyspnoea and difficulty in breathing led to 5.8% - 7.3% of all dispatched ambulances, and was the fourth most frequent cause for the most urgent EMS responses [5,6]. In a Danish study, patients with dyspnoea as cause for dispatching an ambulance were found to have the second highest cumulative mortality rates (1-day: 4.6% and 30-day: 12.3%) among the EMS patients, only surpassed by the symptom of unconsciousness/cardiac arrest [7].

Diagnoses for EMS patients with acute dyspnoea are important to ensure the right treatment. Heart diseases and respiratory diseases have been found to be the most common diagnoses [8,9]. Few studies have reported outcome measurements, but a recent Danish study found that while 30-day mortality rate among EMS patients diagnosed with cardiovascular diseases, decreased from 20.1% in 2007 to 12.2% in 2014, the mortality rate was unchanged and substantial, around 12.5%, during the same period for EMS patients with respiratory diseases.

From the perspective of emergency departments contacts, a recent study found that respiratory diseases were the fifth most common diagnosis given, with the third highest 30-day mortality rate of 8.44%. Furthermore, a peak in the number of patients with respiratory diseases was observed in the very young children, and in the elderly. [10] Another study showed asthma stood out among young, and chronic obstructive pulmonary disease among the elderly patients admitted to an emergency department. [11]

The frequency, mortality, and underrated problem related to breathing difficulty, makes it crucial to study the prehospital patients with breathing difficulties further. Therefore, our aim was twofold, namely

1. to investigate the hospital diagnoses patterns and mortality rates of patients to whom EMS was dispatched due to breathing difficulty.

and

2. to investigate the initial main symptoms at the emergency call and mortality rates for EMS patients diagnosed with respiratory diseases in hospital.

Materials and methods

Ethics

The study was approved by the Danish Data Protection Agency (North Denmark Region record number 2008-58-0028 and project ID number 2016–80). Likewise, The Danish Patient Safety Authority approved the study (3-3013-1675/1) and gave permission to access prehospital patient medical records.

Study design and setting

We performed a population-based historic cohort study on EMS patients to whom emergency ambulances were dispatched following a 1-1-2 call from January 2012 –September 2015.

To aid the interpretation of this study, a brief overview of the Danish prehospital system follows. As a tax supported system, the Danish health care is equally accessible for all citizens, including the prehospital system. The Danish emergency number (1-1-2) calls are answered by the Police, and since 2011, in case of a medical emergency, the call is forwarded to an Emergency Medical Coordination Centre. Here, healthcare professionals assess the severity and need for an ambulance by using a criteria based dispatch guideline, the Danish Index for Emergency Care, [12]. This is divided into 37 criteria corresponding to clinical signs, symptoms or incidents. As such, the healthcare professionals assess what they find to be the main issue over the phone, e.g. dyspnoea or *breathing difficulty* which is criteria number 28. The ambulance personnel do not assign a Danish Index for Emergency Care criteria. Below, we refer to the Danish Index for Emergency Care criteria as symptoms.

Every Danish citizen has a unique civil registration number, which enables linkage between registries and data. The regional Patient Administrative Systems contains data on patients' diagnoses, health issues, and other reasons for contact to health services. The data is listed according to International Classification of Diseases, 10th edition (ICD-10). In Denmark, ICD-10 has been implemented since 1994, and it is required that any patient admitted to a hospital receive a diagnosis within the ICD-10 classifications [13,14].

The study took place in the North Denmark Region, which has approximately 587 000 inhabitants, corresponding to 10% of Denmark's population, living in a combination of primarily rural and urban settings.

Selection of participants

Of North Denmark Region citizens to whom an ambulance was dispatched following an 1-1-2 call, and subsequently brought to a hospital in the period January 2012 –September 2015 (45 months), we included two groups of patients:

1. EMS patients with *breathing difficulty* as the main symptom when calling 1-1-2.
2. EMS patients brought to a hospital by an ambulance after calling 1-1-2, who subsequently received a primary diagnosis within the ICD-10 main chapter X, Diseases of the respiratory system *(Respiratory diseases)*.

If a patient was transported by an emergency ambulance more than once, we only used the patient's first contact in the study period. Patients without a known civil registration number and inter-hospital transportations were not included.

Measurements

The logistic ambulance dispatch system, EVA 2000, provided technical data on dispatched emergency ambulances, symptom when calling 1-1-2, and patient identity (civil registration number). In cases where healthcare professionals did not assign a symptom at the 1-1-2 call, we noted the symptom as *not registered*.

We used the patients' first primary diagnosis given in hospital according to ICD-10, which was retrieved from the regional Patient Administrative System. If a patient was given a non-specific primary diagnosis (ICD-10 main chapters XVIII, Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified *(symptoms and signs)* and XXI, Factors influencing health status and contact with health services *(other factors)*), we searched for a more specific diagnosis during the hospital stay. Data on vital status, i.e. date of death, was retrieved from the Danish Civil Registration System.

Outcomes

The main outcome was 1- and 30-day mortality rates. Patient age, sex, symptom when calling 1-1-2, and primary diagnosis given in hospital, were described.

The study's two groups; patients with the symptom *breathing difficulty* and patients diagnosed with *respiratory diseases*, will be described separately.

Analysis

Data were anonymised for statistical analysis. The results are presented as descriptive statistics with measures of frequency for the distribution of ICD-10 diagnoses and symptoms.

We used the Kaplan-Meier estimator to calculate 1-day and 30-day mortality. Patients who received a diagnosis unmistakably related to the certain death of the patient, were not included (the ICD-10 diagnoses "sudden cardiac death so described", "other ill-defined and unspecified causes of mortality", and the specific Danish code "cardiac death according to the Danish Health Act §176"). The mortality rates are presented as percentages with 95% confidence intervals and cumulative number of deaths. Only symptoms and ICD-10 main chapters with more than 100 patients are presented.

Stata/MP 15.1 (StataCorp LLC, Texas, USA) was used for all statistical analyses.

Results

Characteristics of study subjects

In the study period a total of 102 879 emergency ambulances were dispatched (Fig 1). In total 6 136 were dispatched with *breathing difficulty* as the main symptom. Simultaneously, amongst the total ambulance runs, 6 007 resulted in a hospital contact with *respiratory diseases* as primary diagnosis. After exclusion of missing values, errors and multiple runs (Fig 1.), we included a total of 3 803 EMS patients who called 1-1-2 due to the symptom *breathing problem* and 4 014 EMS patients who were diagnosed with *respiratory diseases* in hospital. There was an overlap of 1 797 EMS patients between the two groups. This overlap is displayed in Fig 2.

The following results are divided separately into the study's two groups.

Main results

EMS patients with breathing difficulty as the main symptom when calling 1-1-2. A total of 3 803 individual patients were identified. Their median age was 69 (Interquartile range 53–79) and 50.0% of them were women.

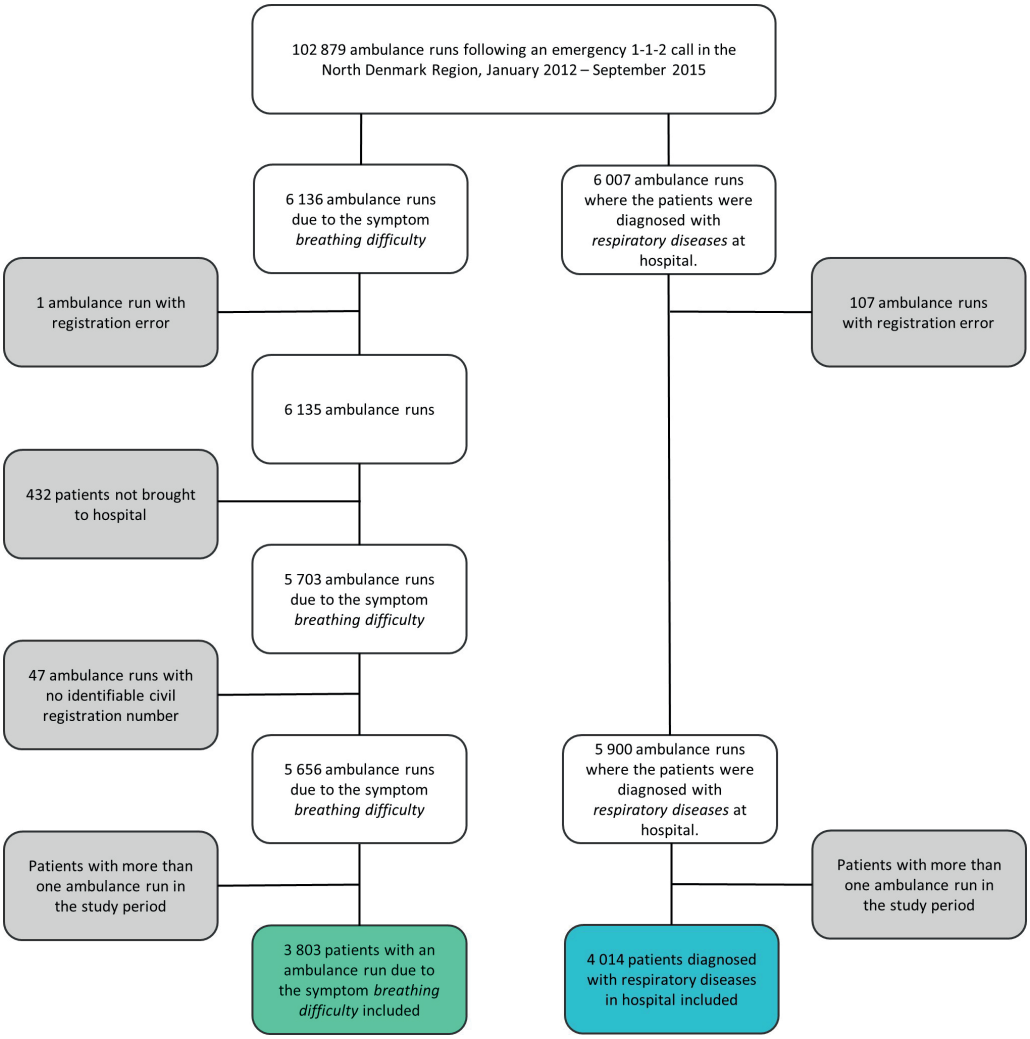

Fig 1. Flowchart for included ambulance runs. The included (white boxes) and excluded (grey boxes) ambulance runs and corresponding number of patients in the study period).

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Nearly half, 47.3% received a primary diagnosis within *respiratory diseases* in hospital. ICD-10 main chapter IX, Diseases of the circulatory system (*circulatory diseases)* constituted 13.4% followed by the non-specific diagnoses: *symptoms and signs* and *other factors* at 12% and 9.6% respectively (Table 1).

ICD-10 main chapter XIX, Injury, poisoning and certain other consequences of external causes (*injuries and poisoning*) and main chapter V, Mental and behavioural disorders (*mental disorders*) were given to 3.4% and 2.8% of the patients with the symptom *breathing difficulty*,

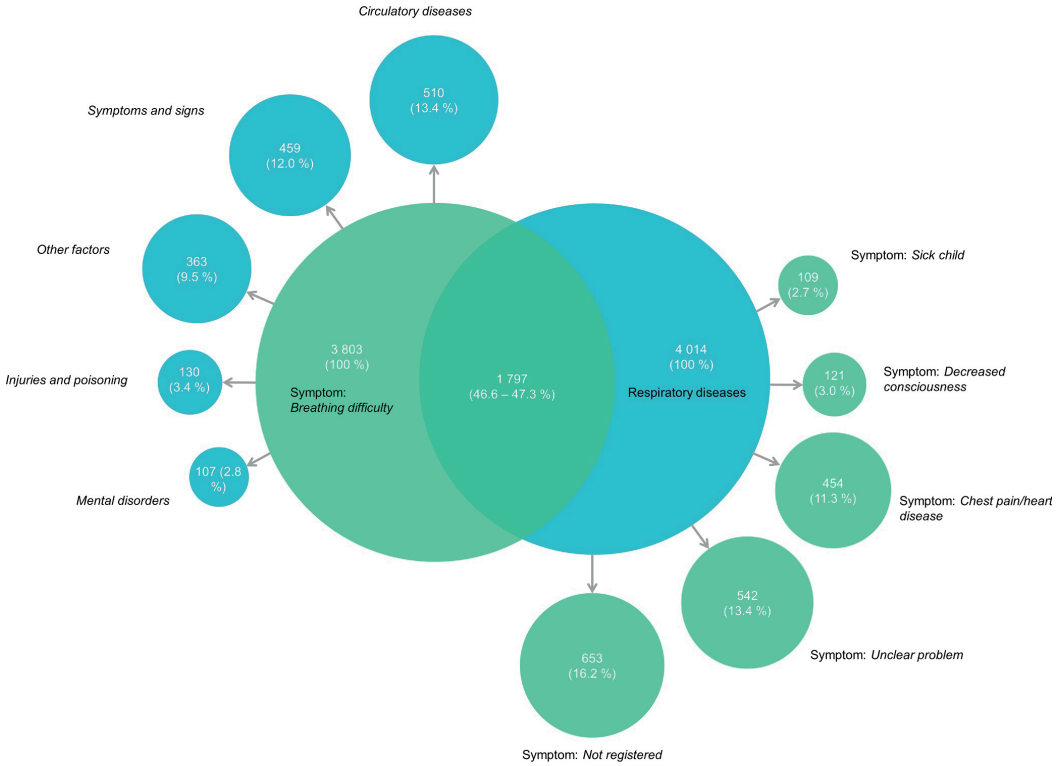

Fig 2. Symptoms and diagnoses overview. Diagram showing the relation between symptoms when calling the emergency number 1-1-2 (green circles) and primary diagnoses given in hospital, following a 1-1-2 call and dispatched ambulance (blue circles). Shows number of patients and percentage of corresponding group. Circle sizes are relative to number of patients.

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most often in young adults, while *respiratory* and *circulatory diseases* increased with age (Fig 3). When looking closer at the diagnoses of *symptoms and signs*, half of the subcategories were related to breathing difficulties, without clear ethology, i.e. R06.0 Dyspnoea and R06.4 Hyperventilation. The highest 1-day and 30-day mortality rates were found within *circulatory diseases* (7.9% and 17.7% respectively), followed by *respiratory diseases* and *other factors* as seen in Table 2. Total number of deaths were highest among *respiratory diseases* with 232 patients, followed by *circulatory diseases* and both *symptoms and signs* and *other factors*. Of all deaths at day 30, only few patients, 0.8% (30 patients), were diagnosed with acute myocardial infarction or cardiac arrest.

EMS patients diagnosed with respiratory diseases in hospital. A total of 4 014 individual patients were identified. The median age was 71 (Interquartile range 57–80) and 46% were women. The initial symptoms when calling 1-1-2 were for the majority *breathing difficulty*, 44.8%, *(*1 797 patients), followed by *unclear problem* with 13.4% and *chest pain* 11.3%. In patients diagnosed with respiratory diseases, 3.0% (121 patients) had the symptom *decreased consciousness* when calling 1-1-2. All symptoms were prominent among patients above 50 years old. Among young children diagnosed with respiratory diseases, the most frequent

Table 1. Primary diagnoses in hospital for patients with symptom breathing difficulty.

Diagnoses	N	Percent
Respiratory diseases	**1 797**	**47.25**
J441: Chronic obstructive pulmonary disease with acute exacerbation, unspecified	459	25.54
J189: Pneumonia, unspecified	363	20.20
J449: Chronic obstructive pulmonary disease, unspecified	185	10.29
J960: Acute respiratory failure	132	7.35
J459: Asthma, unspecified	110	6.12
Circulatory diseases	**510**	**13.41**
I509: Heart failure, unspecified	57	11.18
I489: Atrial fibrillation or atrial flutter, unspecified	53	10.39
I214: Non-STEMI	36	7.06
I219: Acute myocardial infarction, unspecified	31	6.08
I269A: Pulmonary embolism, unspecified	30	5.88
Symptoms and signs	**459**	**12.07**
R060: Dyspnoea	143	31.15
R064: Hyperventilation	91	19.83
R074: Chest pain, unspecified	33	7.19
R539F: Malaise	25	5.45
R559: Syncope or collapse	18	3.92
Other factors	**363**	**9.55**
Z039: Observation for suspected disease or condition, unspecified	229	63.09
Z038: Observation for other suspected diseases and conditions	36	9.92
Z768: Persons encountering health services in other specified circumstances	21	5.79
Z035: Observation for other suspected cardiovascular diseases	19	5.23
Z03: Medical observation and evaluation for suspected diseases and conditions	11	3.03
Injuries and poisoning	**130**	**3.42**
S202: Contusion of thorax	18	13.85
S223: Fracture of rib	11	8.46
T783: Angioneurotic oedema	5	3.85
S060: Concussion	4	3.08
T784: Allergy, unspecified	4	3.08
Mental disorders	**107**	**2.81**
F100: Mental and behavioural disorders due to use of alcohol : acute intoxication	23	21.50
F419: Anxiety disorder, unspecified	18	16.82
F410: Panic disorder [episodic paroxysmal anxiety]	10	9.35
F102: Mental and behavioural disorders due to use of alcohol : dependence syndrome	7	6.54
F101: Mental and behavioural disorders due to use of alcohol : harmful use	5	4.67
Remaining	**437**	**11.49**
Total	**3 803**	**100**

The most frequent primary diagnoses given in hospital according to ICD-10. Includes 3 803 patients who had the symptom breathing difficulty at the emergency 1-1-2 call and an ambulance dispatched. The five most frequent specific diagnoses are included for each main ICD-10 chapter, with percentage of their respective main chapter. ICD-10: International Classification of Diseases, 10th edition.

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symptom (criteria assessed over the phone for dispatching the ambulance) was *sick child* (Fig 4). For 16.2% (653 patients) the symptom was *not registered*, thus we do not know the initial symptom at the emergency call.

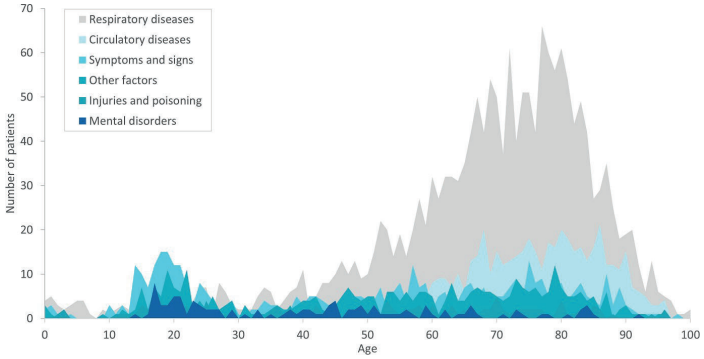

Fig 3. Primary diagnoses in hospital and age. Graph of individual primary diagnoses given in hospital according to ICD-10 main chapters. The graph includes 3 803 patients to whom an emergency ambulance was dispatched due the symptom breathing difficulty. ICD-10: International Classification of Diseases, 10th edition.

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Over-all 1- and 30-day mortality rates was 3.7% and 12.5%. The symptoms *decreased consciousness* had the highest mortality rates of 4.1% and 19.1%, followed by *breathing difficulties*, and *unclear problem* (see Table 3). Mortality rates were similar in patients with symptom *not registered*. Total number of deaths were found to be highest among the symptom *breathing difficulties* (232 patients), followed by *unclear problem*, and *chest pain/heart disease*.

Discussion

We found the most frequent diagnoses given to EMS patients calling 1-1-2 with breathing difficulties, to be *respiratory diseases*, *circulatory diseases*, *symptoms and signs*, and *other factors*. 1- and 30-day mortality rates were over-all 3.4% and 13.2%. For EMS patients diagnosed with *respiratory diseases*, we found that the symptoms *breathing difficulty*, *unclear problem*, and *chest pain/heart disease* were the most frequent. Also, here, the 1- and 30-day mortality rates were similar, over-all 3.7% and 12.5%.

We chose to include both EMS and hospital data which have different coding processes. However, this aided the exhaustiveness and representativeness of the study.

Table 2. Mortality according to diagnoses.

Diagnoses	1-day mortality rate (percent, CI)	Cumulative number of deaths Day 1	30-day mortality rate (percent, CI)	Cumulative number of deaths Day 30
Total	3.40 (2.88 to 4.00)	137	13.21 (12.20 to 14.30)	531
Respiratory diseases	3.62 (2.85 to 4.59)	65	12.95 (11.48 to 14.60)	232
Circulatory diseases	7.91 (5.86 to 10.62)	40	17.65 (14.59 to 21.27)	89
Symptoms and signs	0.88 (0.33 to 2.33)	4	5.77 (3.97 to 8.36)	26
Other factors	3.04 (1.69 to 5.42)	11	9.17 (6.60 to 12.65)	33
Injuries and poisoning	2.31 (0.75 to 6.98)	3	3.86 (1.62 to 9.02)	5
Mental disorders	0.00 (0.00 to 0.00)	0	3.74 (1.42 to 9.65)	4

1- and 30-day mortality for 3 803 patients who had the symptom breathing difficulty at the 1-1-2 call and an ambulance dispatched. Separated by ICD-10 main chapters. CI: 95% Confidence interval. ICD-10: International Classification of Diseases, 10th edition.

https://doi.org/10.1371/journal.pone.0213145.t002

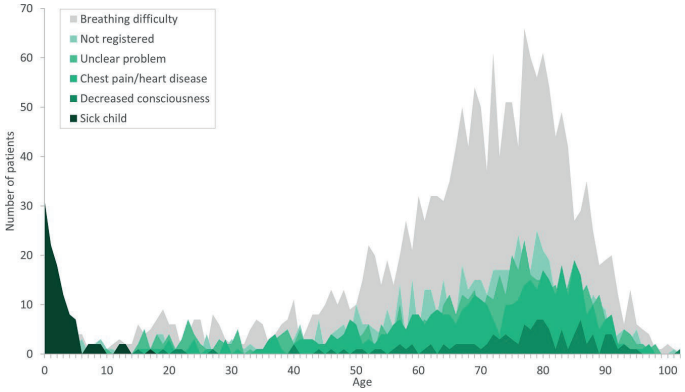

Fig 4. Symptom and age. Graph of individual symptoms when calling 1-1-2 according to age. The graph includes 4 014 patients diagnosed with respiratory diseases in hospital, following an emergency 1-1-2 call and dispatched ambulance.

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For 16% of the patients there was no information on the criteria for dispatching the ambulance possibly because registrations were done manually by the call-takers. The *not registered* symptoms at the emergency call could have contained specific symptoms, resulting in a shift of the frequencies reported in this study. Likewise, it is possible that patients with other symptoms than *breathing difficulties* could have experienced dyspnoea, as it is present in other conditions. A greater level of detail may have been obtained if the patients' medical records were accessed. However, hospital diagnoses are part of the daily clinical practice and registration of acute admissions in the Patient Administrative System have previously been found to have a high validity. [14,15] Furthermore, we used the criteria for dispatching an ambulance, assessed by healthcare professionals at the emergency call. This is the first available data, regarding the situation. More detailed clinical information may have been obtained if the patients' prehospital medical record were accessed, providing information from ambulance personnel in direct contact with the patient, in contrast to the initial phone assessment.

Table 3. Mortality according to symptom.

Hierarchy	1-day mortality rate (percent, CI)	Cumulative number of deaths Day 1	30-day mortality rate (percent, CI)	Cumulative number of deaths Day 30
Total	3.72 (3.16 to 4.37)	148	12.52 (11.51 to 13.62)	480
Breathing difficulty	3.62 (2.85 to 4.59)	65	12.95 (11.48 to 14.60)	232
Unclear problem	2.59 (1.54 to 4.33)	14	13.14 (10.56 to 16.28)	71
Chest pain/heart disease	1.10 (0.46 to 2.63)	5	6.63 (4.68 to 9.35)	30
Decreased consciousness	4.13 (1.74 to 9.64)	5	19.10 (13.13 to 27.34)	23
Not registered	3.98 (2.73 to 5.79)	26	14.90 (12.38 to 17.88)	97

1- and 30-day mortality for 4 014 patients diagnosed with respiratory diseases in hospital, following an emergency 1-1-2 call and ambulance dispatch. Separated by symptom when calling 1-1-2.

CI– 95% Confidence interval.

https://doi.org/10.1371/journal.pone.0213145.t003

Furthermore, the choice of using the patients' first contact in the study period might have resulted in a lower mortality rate, than if the patients' last contact had been used, due to possible repeated users and patients with chronic diseases. Thus, our results concerning mortality is not overestimated. Likewise, the exclusion of patients without a valid civil registration number and patients not brought to a hospital, could have shifted the mortality rates. However, we did not have information of the possible date of death for these patients.

Apart from respiratory diseases, we found that heart diseases are prominent among EMS patients presenting breathing difficulty. This is consistent with studies from the USA [8], Australia and New Zeeland [9], and Germany [16]. However, our study also revealed that non-specific diagnoses were frequently applied to patients with breathing difficulty. A high number of non-specific diagnoses have also been found in previous Danish studies. [10,17] This underlines the complexity of dyspnoea and stresses the need for further research of this patient group in EMS, to gain insight in the patient population that the EMS staff faces.

It is important to note that our study focused on the symptoms as presented at the initial contact, the call to the Emergency Medical Coordination Centre over the phone, which is important because this first assessment of the patient determines the EMS response and patient care pathway. This contrasts with the USA study, where the patients' main symptoms were defined by the EMS personnel on scene. [8] In the Australian and New Zeeland study, it was defined by the emergency department personnel. [9] Finally, in the German study the treating physician specified the patient's chief complaint after arrival to the Emergency Department. [16] The German study also included mortality as an outcome measure and found an in-hospital mortality of 9.4% for patients with dyspnoea as the chief complain. This mortality rate is similar to the 30-day mortality rate of 13% found in the current study.

We found that 13.2% of the patients with the initial symptom *breathing difficulty* were deceased within 30 days from the 1-1-2 call. This is consistent with a recent Danish study which found a 30-day mortality rate of 12.6% (CI: 11.9–13.3) for patients with *breathing difficulty* as the main symptom when calling 1-1-2 [7]. However, we also found that only less than one percent of these patients had diagnoses related to acute myocardial infarction or cardiac arrest. This emphasises the severity of *breathing difficulty* beyond only circulatory diseases.

Our study found *respiratory diseases* increased with age and were prominent among the elderly. This is supported by a study from a USA emergency department, which examined trends in emergency department-use by elderly adults. The study identified shortness of breath and chest pain as the two most common reasons for emergency department visits. [18] With a median age of 69 year for patients with the symptom *breathing difficulty*, and a median age of 71 years for patients diagnosed with *respiratory diseases* in hospital, the elderly represents the majority of patients in this study. The variation in diagnoses according to age groups, is interesting for future studies, due to knowledge needed in emergency departments or intensive care units.

In conclusion, the over-all 30-day mortality rates of 13.2% and 12.5% for the symptom and diagnosis respectively, alongside the distribution of symptoms and diagnoses, suggest the breathing difficulty patient group is complex and has severe health problems. Consequently, these findings may be able to raise awareness towards the patient group, and thereby increase focus on diagnostics and treatment to improve the patient outcome.

Author Contributions

Conceptualization: Tim Alex Lindskou, Laura Pilgaard, Morten Breinholt Søvsø, Torben Anders Kløjgård, Erika Frischknecht Christensen.

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APPENDIX B. PAPER II

Lindskou TA, Weinreich UM, Lübcke K, Kløjgaard TA, Laursen BS, Mikkelsen S, Christensen EF. Patient experience of severe acute dyspnoea and relief during treatment in ambulances: A prospective observational study.

Currently under review at Scandinavian Journal of Trauma, Resuscitation and Emergency Medicine

APPENDIX C. PAPER III

Lindskou TA, Lübcke K, Kløjgaard TA, Laursen BS, Mikkelsen S, Weinreich UM, Christensen EF. Predicting outcome for ambulance patients with dyspnoea – a prospective cohort study.

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